

FIGURE 1

AGGCAGCAGCTGCAGGCTGACCTTGCAGCTGGCGGA**ATGG**ACTGGCCTCACAAACCTGCTGTTCTT
CTTACCATTCATCTTCCCTGGGCTGGGCCAGCCCAGGAGCCCCAAAGCAAGAGGAAGGGCAAGGGCG
GCCTGGGCCCTGGCCCTGGCCCTCACCAAGGTGCCACTGGACCTGGTGTACGGATGAAACCGTATGCC
GCATGGAGGAGTATGAGAGAACATCGAGGAGATGGTGGCCAGCTGAGGAACAGCTCAGAGCTGGCCAG
AGAAAGTGTGAGGTCAACTGCAGCTGTGGATGTCCAACAAGAGGAAGCCTGTCTCCCTGGGCTACAGCAT
CAACCACGACCCAGCCGTATCCCCGTGGACCTGCCGGAGGCACGGTGCCTGTCTGGCTGTGAACC
CCTTCACCATGCAGGAGGACCGCAGCATGGTAGCGTGCCGGTGTTCAGCCAGGTTCTGTGCGCCGCCGC
CTCTGCCGCCACCGCCCCCACAGGGCCTTGCCTGCCAGCGCGCAGTCATGGAGACCATCGCTGTGGCTG
CACCTGCATCTCT**TGA**ATCACCTGGCCAGAAGCCAGGCCAGCAGCCGAGACCATCCTCCTGCACCTT
GTGCCAAGAAAGGCCTATGAAAAGTAAACACTGACTTTGAAAGCAAG

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FIGURE 2

MDWPHNLLFLLTISIFLGLGQPRSPKSKRKGQGRGPLAPGPHQVPLDLVSRMKPYARMEYERNIEEMVA
QLRNSSELAQRKCEVNLQLWMSNKRSLSPWGYSINHDPSRIPVDLPEARCLCLGCVNPFTMQEDRSMVSVP
VFSQPVRRRLCPPPRTGPCRQRAVMETIAVGCTCIF

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FIGURE 3

GCCAGGTGTGCAGGCCGCTCCAAGCCCAGCCTGCCCGCTGCCGCCACC **ATG**ACGCTCCTCCCCGGCCTCC
TGTTCTGACCTGGCTGCACACATGCCTGCCACCAGACCCCTCCCTCAGGGGGCACCCCCACAGTCAC
GGTACCCCACACTGCTACTCGGCTGAGGAACAGCCTCGGCCAGGCCCCCACACCTGCTGGCTGAGG
TGCCAAGTGGGGCAGGCTTGCCTGTAGCCCTGGTGTCCAGCCTGGAGGCAGCAAGCCACAGGGGGAGGC
ACGAGAGGCCCTCAGCTACGACCCAGTGCCTGGCTGCGGCCGGAGGGTGTGGAGGCAGACACCCAC
CAGCGCTCCATCTCACCTGGAGATACCGTGTGGACACGGATGAGGACCGCTATCCACAGAAGCTGGCCTT
CGCCGAGTGCCTGTGCAGAGGCTGTATCGATGCACGGACGGGCCCGAGACAGCCTGCGCTCAACTCCGTGC
GGCTGCTCCAGAGCCTGCTGGTGTGCCTGGCCCTGCTCCCGCAGGGCTGGGCTCCCCACACCT
GGGGCTTTGCCTTCCACACCGAGTTCATCCACGTCCCCGTGGCTGCACCTGCGTGTGCTGCCCGTTCAAGT
GTGACCGCCGAGGCCGTGGGGCCCTAGACTGGACACGTGTGCTCCCCAGAGGGCACCCCCATTATGTG
TATTATGTTATTATGCCTCCCCAACACTACCCCTGGGTCTGGCATTCCCCTGTCTGGAGGAC
AGCCCCCACTGTTCTCCATCTCCAGCCTCAGTAGTTGGGGTAGAAGGAGCTCAGCACCTTTCCAGC
CCTTAAAGCTGCAGAAAAGGTGTACACGGCTGCCTGTACCTTGGCTCCCTGCTCCGGCTCCCT
TACCCCTATCACTGGCTCAGGCCCGCAGGCTGCCTCTCCCAACCTCCTTGAAGTACCCCTGTTCTTA
AACAAATTATTAAGTGTACGTGTATTAAACTGATGAACACATCCCCAAAA

4003017, 2560074

FIGURE 5

GGCTTGCTGAAAATAAAATCAGGACTCCTAACCTGCTCCAGTCAGCCTGCTTCCACGAGGCCTGTCAGTCA
GTGCCCGACTTGTGACTGAGTGTGCAGTGCAGCAGTACCTGCTGAGGGTGGAGGGAGGCCAAGCTGCCAGGTTGGGCTGG
GTGCTGAGAGGGAGAGGAGCAGAGATGCTGCTGAGGGTGGAGGGAGGCCAAGCTGCCAGGTTGGGCTGG
GGGCCAAGTGGAGTGAGAACTGGGATCCCAGGGGGAGGGTGCAGATGAGGGAGCGACCCAGATTAGGTGA
GGACAGTTCTCTCATTAGCCTTCTACAGGTGGTTGCATTCTGGCAATGGTCAATGGGAACCCACACCT
ACAGCCACTGGCCAGCTGCTGCCAGCAAAGGCAGGACACCTCTGAGGAGCTGCTGAGGTGGAGCACT
GTGCCCTGTGCCCTCCCTAGAGCCTGCTAGGCCAACGCCACCCAGAGTCCTGTAGGGCCAGTGAAGATGGA
CCCCTCAACAGCAGGGCCATCTCCCCCTGGAGATATGAGTTGGACAGAGACTTGAACCGGCTCCCCAGGA
CCTGTACCACGCCGTTGCCGTGCCCCACTGCGTCAGCCTACAGACAGGCTCCCACATGGACCCCCGGG
GCAACTCGGAGCTGCTCTACCACAAACCAGACTGTCTTCTACAGGCAGGCTGCCATGGCAGAAGGGCACC
CACAAGGGCTACTGCCTGGAGCGCAGGCTGTACCGTGTTCCTTAGCTTGTGTGTGCGGGCCCCGTGT
GATGGGCTAGCCGGACCTGCTGGAGGCTGGTCCCTTTGGGAAACCTGGAGCCAGGTGTACAACCACCTG
CCATGAAGGGCCAGGATGCCAGATGCTTGGCCCTGTGAAGTGCTGTGGAGCAGCAGGATCCGGGAC
AGGATGGGGGGCTTGGGAAAACCTGCACTTCTGCACATTGAAAAGAGCAGCTGCTGCTTAGGGCCGC
CGGAAGCTGGTGTCCCTGTCATTCTCTCAGGAAAGGTTCAAAGTCTGCCATTCTGGAGGCCACCA
CTCCTGTCTCTCCCTTTCCATCCCTGCTACCTGGCCAGCACAGGCACCTTCTAGATATTC
CTTGGCTGGAGAAGAAAGAGCCCTGGTTTATTGTTACTCATCACTCAGTGAGCATCTACTTGG
GTGCATTCTAGTGTAGTTACTAGTCTTGTGACATGGATGATTCTGAGGGAGGAAGCTGTTATTGAATGTATA
GAGATTATCCAAATAATCTTATTAAAAATGAAAAA

FIGURE 9

CAACTGCACCTCGTTCTATCGATAGCCACCAGCGAAC**ATG**ACAGTGAAGACCCCTGCATGGCCCAGCCAT
GGTCAAGTACTTGCTGCTGTCGATATTGGGGCTTGCCTTCTGAGTGAGGCAGCTCGGAAAATCCCCA
AAGTAGGACATACTTTTCCAAAAGCCTGAGAGTTGCCCGCCTGTGCCAGGAGGTAGTATGAAGCTTGAC
ATTGGCATCATCAATGAAAACCAGCGCTTCCATGTCACGTAACATCGAGAGCCGCTCACCTCCCCCTG
GAATTACACTGTCACTTGGGACCCCAACCGTACCCCTCGGAAGTTGTACAGGCCAGTGTAGGAACCTGG
GCTGCATCAATGCTCAAGGAAAGGAAGACATCTCCATGAATTCCGTTCCATCCAGCAAGAGACCCCTGGTCGTC
CGGAGGAAGCACCAAGGCTGCTCTGTTCTTCAGTTGGAGAAGGTGCTGGTACTGTTGGCTGCACCTG
CGTCACCCCTGTCATCCACCATGTGCAGTAAGAGGTGCATATCCACTCAGCTGAAGAAG

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FIGURE 10

MTVKTLHGPAMVKYLLLSILGLAFLSEAAARKIPKVGHFFQKPESCPPVPGGSMKLDIGIINENQRVSMS
RNIESRSTSPWNYTVTWDPNRYPSEVVQAQCRNLGCINAQGKEDISMNSVPIQQETLVVRRKHQGCSVSFQ
LEKVLVTVGCTCVTPVIHHVQ

Signal sequence: Amino acids 1-30

N-glycosylation site: Amino acids 83-86

N-myristoylation sites: Amino acids 106-111;136-141

4000152 10300

FIGURE 11

CCGGCGATGTCGCTCGTGTGCTAACGCTGGCCGCGCTGTGCAGGAGCGCCGTACCCCGAGAGCCGACCGT
TCAATGTGGCTCTGAAACTGGGCCATCTCCAGAGTGGATGCTACAACATGATCTAATCCCCGGAGACTTGA
GGGACCTCCGAGTAGAACCTGTTACAACACTAGTGTGCAACAGGGACTATTCAATTGTGATGAATGTAAGC
TGGGTACTCCGGGCAGATGCCAGCATCGCCTGTTGAAGGCCACCAAGATTGTGACGGGCAAAGCAA
CTTCCAGTCCTACAGCTGTGAGGGTCAATTACACAGAGGCCCTCAGACTCAGACCAGACCCTCTGGTG
GTAATGGACATTTCCTACATCGGCTTCCCTGTAGAGCTGAACACAGTCTATTCTATTGGGCCATAAT
ATTCTTAATGCAAATATGAATGAAGATGGCCCTTCATGTCGTGAAATTTCACCTCACCAAGGCTGCTAGA
CCACATAATGAAATATAAAAAAGTGTGCAAGGCCGAAGCCTGTGGATCCGAACATCACTGCTTGT
AGAAGAATGAGGAGACAGTAGAAGTGAACCTCACACCCTCCCTGGGAAACAGATACTGGCTTTATC
CAACACAGCACTATCATCGGTTTCTCAGGTGTTGAGCCACACCAGAAGAAACAAACGGCAGCTTCAGT
GGTGAATCCAGTGACTGGGATAGTGAAGGTGCTACGGTCAGCTGACTCCATATTTCCTACTTGCGCA
GCGACTGCATCCGACATAAGGAACAGTTGTGCTCTGCCACAAACAGGCGTCCCTTCCCTGGATAAC
AACAAAAGCAAGCCGGGAGGCTGGCTGCCTCTCCTCTGCTCTGCTGGTGGCCACATGGGTGCTGGT
GGCAGGGATCTATCTAATGTGGAGGCACGAAAGGATCAAGAAGACTCCTTTCTACCACACACTACTGC
CCCCCATTAAGGTTCTGTGGTTACCCATCTGAAATATGTTCCATCACACAATTGTTACTTCACTGAA
TTTCTCAAAACCATTGCAGAAGTGGATCTGCTCTGAAAGTGGCAGAAAAGAAAATAGCAGAGATGGG
TCCAGTGCAGTGGCTGCCACTCAAAAGAAGGCAGCAGACAAAGTCGCTTCCCTCTTCCAATGACGTCA
ACAGTGTGCGATGGTACCTGTGGCAAGAGCGAGGGCAGTCCAGTGAGAACTCTCAAGACCTTCCCC
CTTGCCTTAAACCTTCTGAGTCAAGAAGCCAGATTCTGCACAAATACGTGGTGGTCACTT
TAGAGAGATTGATAACAAAAGACCATTACAATGCTCTGAGTCAAGCAGCAGGTGTCAGCAGGAAAAGATCACAAGCCTGC
CCACTGCTTCTGTGCAGAACCTCCATGTCAAGCAGCAGGTGTCAGCAGGAAAAGATCACAAGCCTGC
CACGATGGCTGCTCCTGTAG

FIGURE 12

MSLVLLSLAALCRSAVPREPTVQCGSETGPSPEWMLQHDLIPGDLRDLRVEPVTTSVATGDYSILMNVS WV
LRADASIRLLKATKICVTGKSNFQSYSCVRCNYTEAFQTQTRPSGGKWTFSYIGFPVELNTVYFIGAHNIP
NANMNEGPSMSVNFTSPGCLDHIMKYKKKCVKAGSLWDPNITACKNEETVEVNFTTPLGNRYMALIQH
STIIGFSQVFEPHQKKQTRASVVIPTVGDSEGATVQLTPYFPTCGSDCIRHKGTVVLCPQTGVFPFLDN NK
SKPGGWLPLLLLSLLVATWVLVAGIYLMWRHERIKKTSFSTTLLPPIKVLVVYPSEICFHHTICYFTEFL
QNHCRCSEVILEKWQKKKIAEMGPVQWLATQKKAADKVVFLLSNDVNSVCDGTCGKSEGSPSENSQDLFPLA
FNLFCSDLRSQIHLHKYVVVYFREIDTKDDYNALSVCPKYHLMKDATAFCAELLHVKQQVSAGKRSQACHD
GCCSL

Signal sequence: Amino acids 1-14

Transmembrane domain: Amino acids 290-309

N-glycosylation sites: Amino acids 67-70;103-106;156-159;
183-186;197-200;283-286

cAMP- and cGMP-dependent protein kinase phosphorylation sites:
Amino acids 228-231;319-322

N-myristoylation site: Amino acids 116-121

Amidation site: Amino acids 488-491

FIGURE 13

ACAC TGG CAA AAC AAA ACG AA AG CACT CCG TGT GG AAG TAG GAG GAG A GTC AGG ACT CCC AGG A CAG AG
 AGT GC AC AA ACT ACC CAG CAC AG CCCC CT CG CCCC CT TG GAG GCT GA AG AG GG ATT CC AG CCCC CT GC CA
 CCC AC AG AC AC GGG CT GACT GGG GT CT GCCCC CT TG GGG GGG GGG CAG CAC AG GG CT CAG GCT GGG GT
 GCC AC CT GG CAC CT AGA AG **ATG** C CT GT GC CC CT GG TT CT GCT GT C CT TG GACT GGG CCA AG GCC AGT GG
 TC CTT CT CT GG AG AG GCT GT GGG C CT CAG GAC GCT ACC CACT GCT CT CG GCT CT C CT TG C CC GCT AC
 TGG GAC AGT GAC A TA CT CG C CT G C CT GGG AC AT CG T G C CT GCT CC GGG C CC GT GCT GG C CT AC GCA
 CCT G CAG AC AG AG CT GG T GCT GAG GT G C CAG A AGG AG ACC GACT GT GAC CT TG C AG CT TG C TG G GCT
 ACT TGG C G T G C AT GGG C ACT GGG AAG AG G C CT GA AG AT GAG GAA AG T T G GAG GAG CAG CT GACT CAG G
 GT GG AG GAG C C T AG G A AT G C CT CT CC AGG C C A AG T C GT GCT CT C CT CC AGG C C T ACC C T ACT G C C C
 CT G C G C CT TG GAG GT G C A AG T G C CT G C TG C CC CT TG G C AG T T G G T C AG T CT GT GGG C T CT G G T T A T A T
 GACT G C T T C GAG G C T G C C T A G G G A G T GAG G T A C G A A T C T G G T C C T A A T C T CAG G C C A G G T A C G A G A A G G A
 ACT C A A C C A C A C A C A G C A G C T G C C T G C C C T G C C T G G C T C A A C G T G C A G C A G A T G G T G A C A A C G T G C A T C
 TGG T T C T G A A T G T C T G A G G A G C A G C A C T T C G G C T C T C C C T G T A C T G G A A T C A G G T C C A G G G C C C C C A
 A A A C C C C G G T G G C A C A A A A C C T G A C T G G A C C G C A G A T C A T T A C C T G A A C C A C A C A G A C C T G G T T C C C T G
 C C T C T G T A T T C A G G T G T G G C C T C T G G A A C C T G A C T C C G T T A G G A C G A A C A T C T G C C C T T C A G G G A G G A C C
 C C C G C G C A C A C C A G A A C C T C T G G C A A G C C G C C G A C T G C G A C T G C T G A C C C T G C A G A G C T G G C T G C T G G A C
 G C A C C G T G C T G C T G C C C G C A G A G C G G C A C T G T G C T G G C G G C T C G G G T G G G G A C C C T G C C A G C C A C T
 G G T C C C A C C G C T T C C T G G G A A C C G T C A C T G T G G A C A A G G T T C T G G A C T G G T C C C A T T G C T G A A A G G C C A C C
 C T A A C C T C T G T G T T C A G G T G A A C A G C T C G G A G A A G C T G C A G C T G C A G G A G T G C T T G T G G G C T G A C T C C C T G
 G G G C C T C T C A A A G A C G A T G T G C T A C T G T G G A G A C A C G A G G C C C C A G G A C A A C A G A T C C C T C T G T G C C T T
 G G A A C C C A G T G G C T G T A C T C A C T A C C C A G G A A A G C C T C A C G A G G G C A G C T C G C C T T G G A G A G T A C T T A C
 T A C A A G A C C T G C A G T C A G G C C A G T G T C T G C A G C T A T G G G A C G A T G A C T T G G G A G C G C T A T G G G C T G C C C C
 A T G G A C A A A T A C A T C C A C A A G C G C T G G G C C C T C G T G T G G C T G G C T G C C T A C T C T T G C C G C T G C G C T T T C
 C C T C A T C C T C C T C T C A A A A G G A T C A C G C G A A A G G G T G G C T G A G G C T C T T G A A A C A G G A C G T C C G C T C G G
 G G G C G C C G C C A G G G C C G C G C G G C T C T G C T C C T A C T C A G C C G A T G A C T C G G G T T T C G A G G C G C T G G T G
 G G C G C C C T G G C G T C G G C C T G T G C C A G C T G C C G C T G C G C G T G G C C G T A G A C C T G T G G A G C C G T C G T G A A C T
 G A G C G C G C A G G G C C C G T G G C T T G G T T C A C G C G C A G C G G C C A G A C C C T G C A G G A G G G C G G C G T G G T G G
 T C T T G C T C T C T C C C G G T G C G G T G G C G T G T G C A G C G A G T G G C T A C A G G A T G G G G T G C C G G G C C C G G G
 G C G C A C G G C C C G C A C G A C G C C T T C C G C G C T C G C T C A G C T G C G T G C T G C C C G A C T T C T G C A G G G C C G G G C
 G C C C G G C A G C T A C G T G G G G C C T G C T C A G C A G G C T G C T C C A C C C G A C G C C G T A C C C G C C T T T C C G C A
 C C G T G C C C G T C T C A C A T G C C C T C C C A A C T G C C A G A C T T C T G G G G C C C T G C A G C A G C C T C G C G C C C G
 C G T T C C G G G C G G C T C C A A G A G A G G C G G A G C A A G T G T C C C G G C C C T G C A G C A G C C T G G A T A G C T A C T T
 C C A T C C C C C G G G G A C T C C C G C G C G G G A C G C G G G T G G G A C C A G G G G C G G G A C C T G G G G C G G G G A C G G G A
 C T T A A A A A A G G C A G A C G C T G T T T C T A A A A A A

FIGURE 14

MPVPWFLLSLALGRSPVVLSLERLVGPQDATHCSPGLSRLWDSDILCLPGDIVPAPGPVLAPTHLQTELV
LRCQKETDCDLCLRVAVHLAVHGHWEEPEDEEKFGGAADSGVEEPRNASLQAQVVLFSQAYPTARCVLLEV
QVPAALVQFGQSVGSVYDCFEAALGSEVRIWSYTQPRYEKELNHTQQLPALPWLNVSADGDNVHLVLNVS
EEQHFGLSLYWNQVQGPPKPRWHKNLTGPQIITLNHTDLVPCLCIQVWPLEPDSVRTNICPFREDPRAHQN
LWQAARLRLLTQSWLLDAPCSLPAEAALCWRAPGGDPCQPLVPPLSWENVTVDKVLEFPLLKGHPNLCVQ
VNSSEKLQLQECLWADSLGPLKDDVLLLETRGQPQDNRSLCALEPSGCTSLSKASTRAARLGEYLLQDIQS
GQCLQLWDDDLGALWACPMKYIHKRWALVWLACLLFAAALSLILLKKDHAKGWLRLLKQDVRSGAAARG
RAALLLYSADDSGFERLVGALASALCQLPLRVAVDLWSRELSAQGPVAWFHAQRRQTLQEGGVVVLLFSP
GAVALCSEWLQDGVSGPGAHGPHDAFRASLSCVLPDFLQGRAPGSYVGACFDRLLHPDAVPALFRTVPVFT
LPSQLPDFLGALQQPRAPRSGRLQERAEQVSRALQPALDSYFHPPGT PAPGRGVGPGAGPGAGDGT

signal sequence: Amino acids 1-20

transmembrane domain: Amino acids 453-473

N-glycosylation sites: Amino acids 118-121;186-189;198-201;
211-214;238-241;248-251;334-337;
357-360;391-394

Glycosaminoglycan attachment site: Amino acids 583-586

cAMP- and cGMP-dependent protein kinase phosphorylation site:
Amino acids 552-555

N-myristoylation sites: Amino acids 107-112;152-157;319-324;
438-443;516-521;612-617;692-697;
696-701;700-705

FIGURE 16

MGSSRLAALLLPLLIVIDLSAGIGFRHLPHWNTRCPLASHTDDSGTGSAYIPCRTWWALFSTKPWCVRVWHCSRCLCQHLLSGGSGLQRGLFHLLVQKSKKSTFKFYRRHKMPAPAQRKLLPRRHLSEKSHHISIPSPDISHKGLRSKRTQPSDPETWESLPRLDSQRHGGPEFSFDLLPEARAIRVTISSLGPEVSVRLCHQWALECEELSSPYDVQKIVSGGHTVELPYEFLPCLCIEASYLQEDTVRRKKCPFQSWPEAYGSDFWKSVHFTDYSQHTQMVMALTLRCPPLKLEAALCQRHDWHTLCKDLPNATARESDGWYVLEKVDLHPQLCFKFSFGNSSHVECPHQTGSLSWNVSMDTQAQQQLILHFSSRMHATFSAAWSLPGLGQDTLVPPVYTVSQARGSSPVSDLIIPFLRPGCCVLLVWRSDVQFAWKHLLCPDVSYRHLGLLALLALLTLLGVVLALTCCRQPQSGPGPARPVLLHAADSEAQRRLVGALAEALLRAALGGGRDVIVDLWEGRHVARVGPLPWLAARTRVAREQGTVLLWSGADLRPVSGPDPRAPLLALLHAAPRPLLAYFSRLCAKGDIAPPRLALPRYRLLRDLPRLLRALDARPFAEATSWGRLGARQRRQSRLELCSRLEREAARLADLG

Signal peptide: Amino acids 1-23

Transmembrane domain: Amino acids 455-472

N-glycosylation sites: Amino acids 318-322; 347-351; 364-368

Glycosaminoglycan attachment site: Amino acids 482-486

cAMP- and cGMP-dependent protein kinase phosphorylation sites:
Amino acids 104-108; 645-649

Tyrosine kinase phosphorylation site: Amino acids 322-329

N-myristoylation sites: Amino acids 90-96; 358-364; 470-476

Eukaryotic cobalamin-binding proteins: Amino acids 453-462

FIGURE 17

40000-140000
GCCAGGCCCTATCTCCCTGCCAGGAGGCCGGAGTGGGGGAGGTCAAGACGGGGCGGTTGGAGGGGAGGG**AT**
GCCACCGCCTCTGCCTCAGGTGTTCTGCCTGCAGTGGAGAGCAGGGAGTGGGCCAGCCAGCA
GAAACAGTGGCTGTACAACATCACCTCAAATATGACAATTGTACCACCTACTGAATCCAGTGGCAAGT
CATGTGATTGCTGACGCCAGAATATCACCACGCCAGTATGCTTGCCTGACCAAGTGGCAAGT
TCTTGGTCCCCAGGGGCCCTCGGCATCGAATTCTGAAAGGATTTCGGTAATACTGGAGGAGCTGAAGT
CGGAGGGAAAGACAGTGCCAACAACTGATTCTAAAGGATCCGAAGCAGCTAACAGTAGCTCAAAAGAACT
GGAATGGAATCTCAACCTTCCTGAATATGAAATTGAAACGGATTATTCGTAAGGTTGTCCCTTCC
TTCCATTAAAAAGAAAGCAATTACCAACCTTCTTCTAGAACCGAGCCTGTGACCTGTTACAGC
CGGACAATCTAGCTGTAAACCCCTCTGGAAGCCTCGAACCTGAACATCAGCCAGCATGGCTCGGACATGC
AGGTGTCCTCGACCACGCACCGCATGGCTGGACATGCAGGTGTCCCTCGACCACGCACCGCACAACCTC
GGCTTCCGTTCTTCTATCTTCACTACAAGCTCAAGCAGAAGGACCTTCAAGCAGAAAGACCTGTAAGCA
GGAGCAAACACTACAGAGATGACCAGCTGCCCTCCTCAAAATGTTCTCCAGGGATTATATAATTGAGCTGG
TGGATGACACTAACACAAGAAAAGTGATGCATTATGCCCTAAAGCCAGTGCACCTCCGTGGCCGGG
CCCATCAGAGGCCGTGGCCATCACAGTGCCTGGTAGTCATATCGGCATTCGCGACGCTTCACTGTGAT
GTGCCGAAGAAGCAACAAGAAAATATATTACACATTAGATGAAGAGAGCTTGAGTCTCCACATACA
CTGCAGCACTCCCAAGAGAGAGGCTCCGGCCGGCGAAGGTCTTCTGCTATTCCAGTAAAGATGGC
CAGAACATGAATGTCGTCAGTGCCTCTGTAGAGAAGGGCAGAGAGAATGGTCATCCAGAAGATCCACGAGT
CCCAGTTCATCATTGTGGTTGTTCAAAGGTATGAAGTACTTGTGGACAAGAAGAACTACAAACACAAA
GGAGGTGGCCGAGGGCTCGGGAAAGGGAGAGCTCTTCCCTGGTGGCGGTGTCAGCCATTGCCGAAAGCTCCG
CCAGGCCAAGCAGAGTTCGTCGCCGGCTCAGCAAGTTATGCCGTACTTGTGATTATTCTCGCAGG
GAGACGTCCCCGGTATCCTAGACCTGAGTACCAAGTACAGACTCATGGACAATCTCCTCAGCTGTTCC
CACCTGCACTCCCGAGACCACGCCCTCAGGAGGCCGGCAGCACACGCACAGGCAGCAGAAAGGAAC
CTTCCGGAGCAAGTCAGGCCGGTCCCTATACGTCGCCATTGCAACATGCACCAGTTATTGACGAGGAGC
CCGACTGGTTCGAAAAGCAGTTGTTCCCTCATCCTCCTCACTGCGTACCGGGAGCCAGTCTGGAG
AAATTGATTGGCTTGGTTAAATGATGTCATGTGCAAACCAGGGCTGAGAGTGACTTCTGCCCTAA
GGTAGAGGGCTGTTCTTGGGCAACCGGACCAGCCGACTCCAGCACGAGAGTCAGCATGGGGCTGG
ACCAAGACGGGAGGCCGGCTGCCCTTGACGGTAGGCCGCCCTGCAACCCCTGCTGCACACGGTAAA
GCCGGCAGCCCCCTGGACATGCCGGGACTCAGGCATCTGACTCGTCTGTGCCCTCATCCAGCTGTC
TCTGCCACTGATGGAAGGACTCTGACGGACCAGACAGAAACGTCTCCCTGACGGAGAGCGTGTCCCT
CTTCAGGCCCTGGGTGAGGAGGAACCTCTGCCCTTCCAAGCTCCTCTTGTGAGGTCATGCAAAGCA
GATCTGGTTGCCAGCTACACTGATGAACTCCACGCCGGCTGGGTTGTAACAAAAGAAAGAGTCTA
AGCATTGCCACTTAAAAAAAAAAAAAAAAAAAAAA

FIGURE 15

CGAGGGCTCCTGCTGGTACTGTGTCGCTGTCACAGCAAGGCCCTGCCACCCACCTTCAGGCCATGCAG
 CCATGTTCCGGGAGCCCTAATTGCACAGAAGCCC**AT****GGGAGCTCCAGACTGGCAGCCCTGCTCCTGCCTC**
 TCCTCCTCATAGTCATGACCTCTGACTCTGCTGGGATTGGCTTCGCCACCTGCCCACTGGAACACC
 CGCTGTCCCTGGCCTCCACACGGATGACAGTTTCACTGGAAGTTCTGCCTATATCCCTGCCGACCTG
 GTGGCCCTCTTCTCCACAAAGCCTGGTGTGCGAGTCTGGCACTGTTCCCTGGTGCAGAAATCCAAAAAGTCTCCACA
 TTCAAGTTCTATAGGAGACACAAGATGCCAGCAGCTGCTCAGAGGAAGCTGCTGCCCTGTCACCTGTC
 TGAGAAGAGCCATCACATTCCATCCCCTCCCCAGACATCTCCCACAAGGGACTCGCTCTAAAGGACCC
 AACCTCGGATCCAGAGACATGGAAAGTCTCCAGATTGGACTCACAAAGGCATGGAGGACCGAGTTC
 TCCCTTGATTTGCTGCCCTGAGGCCGGCTATTGGGTGACCATATCTTCAGGCCCTGAGGTCAAGCGTGC
 TCTTGTCAACCAGTGGCACTGGAGTGTGAAGAGCTGAGCAGTCCCTATGATGCCAGAAAATTGTGTCTG
 GGGGCCACACTGTAGAGCTGCCCTATGAATTCCCTCTGCCCTGTGTGCATAGAGGCATCCTACCTGCAA
 GAGGACACTGTGAGGCGCAAAAATGTCCTCCAGAGCTGCCAGAACCTATGGCTCGGACTTCTGGAA
 GTCAGTGCACTTCAGTCACTGACTACAGCCAGCACACTCAGATGGTCACTGCCCTGACACTCCGCTGCCCACTGA
 AGCTGGAAGCTGCCCTGCCCAGAGGCACGACTGGCATACCCCTTGCACAGACCTCCGAATGCCACGGCT
 CGAGAGTCAGATGGTGGTATGTTTGGAGAAGGTGGACCTGCACCCCCAGCTCTGCTCAAGTTCTCTT
 TGGAAACAGCAGCCATGTTGAATGCCCAACCAGACTGGGTCTCTCACATCCTGAAATGTAAGCATGGATA
 CCCAAGCCCAGCAGCTGATTCTCACTTCTCAAGAATGCATGCCACCTTCAGTGCTGCCCTGGAGCCTC
 CCAGGCTTGGGCAGGACACTTGGTCCCCCGTGTACACTGTCAGGCCAGGCCGGGCTCAAGCCCAGT
 GTCACTAGACCTCATTCCTCTGAGGCCAGGGTGTGTCTGGTGTGGCGGTCAAGATGTCCAGT
 TTGCCCTGGAAGCACCTCTGTGTCAGATCTCTTACAGACACCTGGGCTCTGATCCTGGCACTGCTG
 GCCCTCCTCACCTACTGGGTGTTCTGCCCTCACCTGCCGGCCACAGTCAGGCCGGCCAGC
 GCGGCCAGTGCTCCTCTGCACGCCGGACTCGGAGGCCAGCGGCCCTGGTGGAGGCCAGTGCTGCG
 TGCTACGGGCAGCGCTGGCGCGACGTGATCGTGACCTGTGGAGGGAGGCACGTGGCGCG
 'GGGCCCGCTGCCGTGGCTCTGGCGCGCGACCGCGTAGCGCGGAGCAGGGCACTGTGCTGCTGT
 GGAGCGCGCCGACCTCGCCCGGTCAAGCGCCCGACCCCCCGCGCCGCCCCCTGCTGCCCTGCTCCAC
 GCTGCCCGCGCCCGCTGCTGCTGCTGCTACTTCAGTCCTCTGCCCAAGGGCGACATCCCCCGCC
 GCTGCCGCCCCCTGCCCGCTACCGCCTGCTGCCGACCTGCCCGTGTGCTGCCGGCTGGACGCCGG
 CTTTCCAGAGGCCACCAGCTGGGCCCTGGGCCAGGCCAGGCCCTAGAGCTGTG
 AGCCGGCTTGAACGAGAGGCCGGACTTGCAAGACCTAGGTTGAGCAGAGCTCCACCGCAGTCCC
 GGGCTGT

FIGURE 18

MPRASASGVPALFVSGEQGVGPASRNNSGLYNITFKYDNCTTYLNPVGKHVIADAQNITISQYACHDQVAVT
 ILWSPGALGIEFLKGFRVILEELKSEGRQCQQLILKDPKQLNSSFRTGMESQPFLNMKFETDYFVKVVPF
 PSIKNESNYHPFFFTRACDLLLQPDNLACKPFWKPRNLNISQHGSMDMQVSFDHAPHGSDMQVSFDHAPHN
 FGFRFFYLHYKLKHEGPFKRKTCKQEQTTEMTSCLLQNVSQGDYIELVDDTNTRKVMHYALKPVHSPWA
 GPIRAVAAITVPLVVISAFAFLFTVMCRKKQQENIYSHLDEESSESSTYTAALPRERLRPRPKVFLCYSSKD
 GQNHMNVVQCFAYFLQDFCGCEVALDLWEDFSLCREGQREWVIQKIHESQFIIVVCSKGMKYFVDKKNYKH
 KGGGRGSGKGELFLVAVSAIAEKLROAKQSSSAALSKFIAVYFDYSCEGDVPGIILDSTKYRLMDNLPQLC
 SHLHSRDHGLQEPGQHTRQGSRRNYFRSKSGRSLYVAICNMHQFIDEEDWFEKQFVPPFHPPPLRYREPVL
 EKFDGSLVLNDVMCKPGPESDFCLKVEAAVLGATGPADSQHESQHGGLDQDGGEARPALDGSAAHQPLLHTV
 KAGSPSDMPRDGSIYDSSVPSSESLPLMEGLSTDQTETSSLTESVSSSSGLGEEEPALPSKLLSSGSC
 ADLGCRSYTDELHAVAPL

Transmembrane domain: Amino acids 283-307

N-glycosylation sites: Amino acids 31-34; 38-41; 56-59;
 113-116; 147-150; 182-185; 266-269

~~Glycosaminoglycan attachment sites: Amino acids 433-436; 689-692~~

cAMP- and cGMP-dependent protein kinase phosphorylation:
 Amino acids 232-235

Tyrosine kinase phosphorylation sites: Amino acids 312-319; 416-424

N-myristoylation site: Amino acids 19-24; 375-380; 428-433;
 429-434; 432-437; 517-522; 574-579;
 652-657; 707-712

FIGURE 19

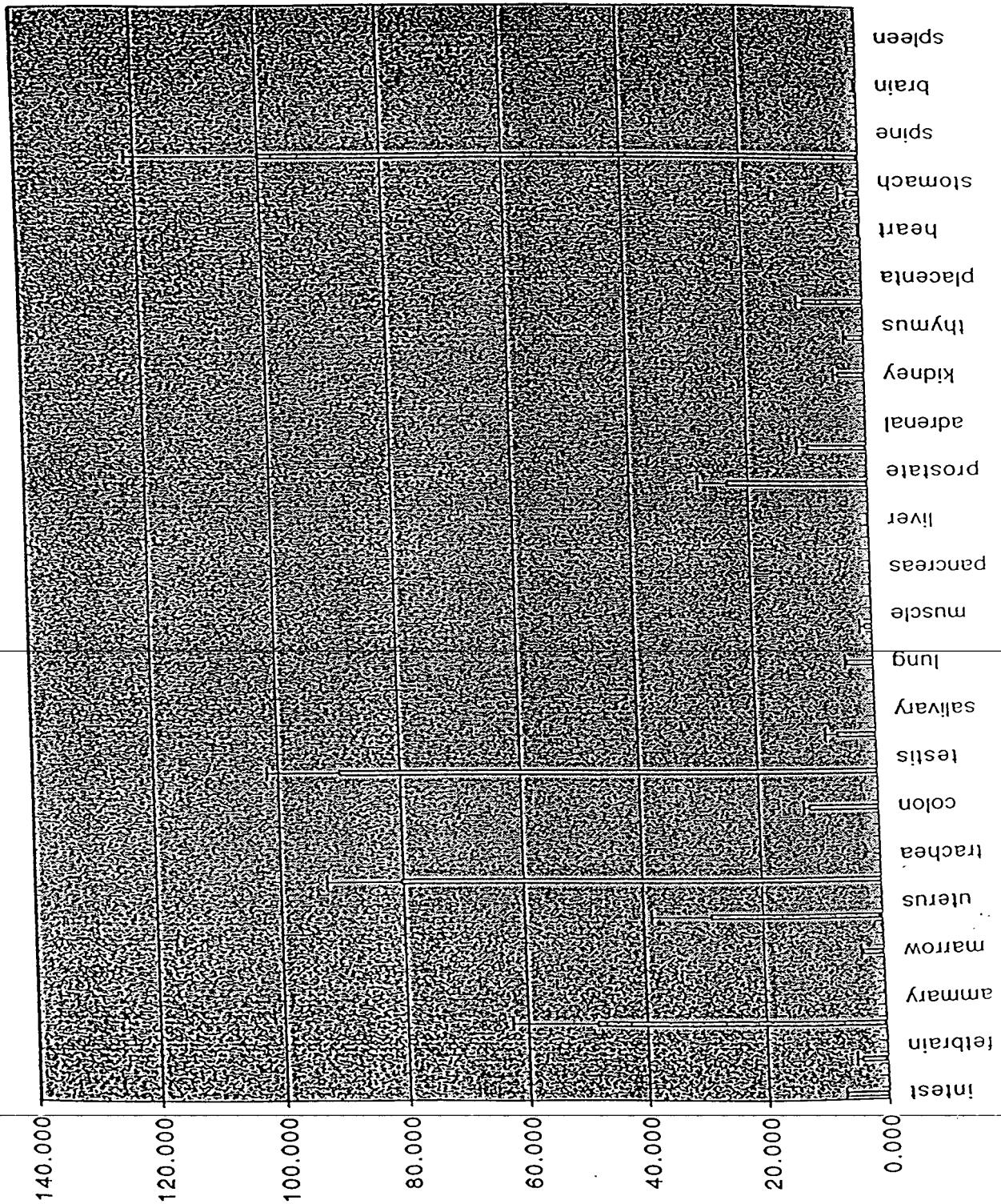
FIGURE 20

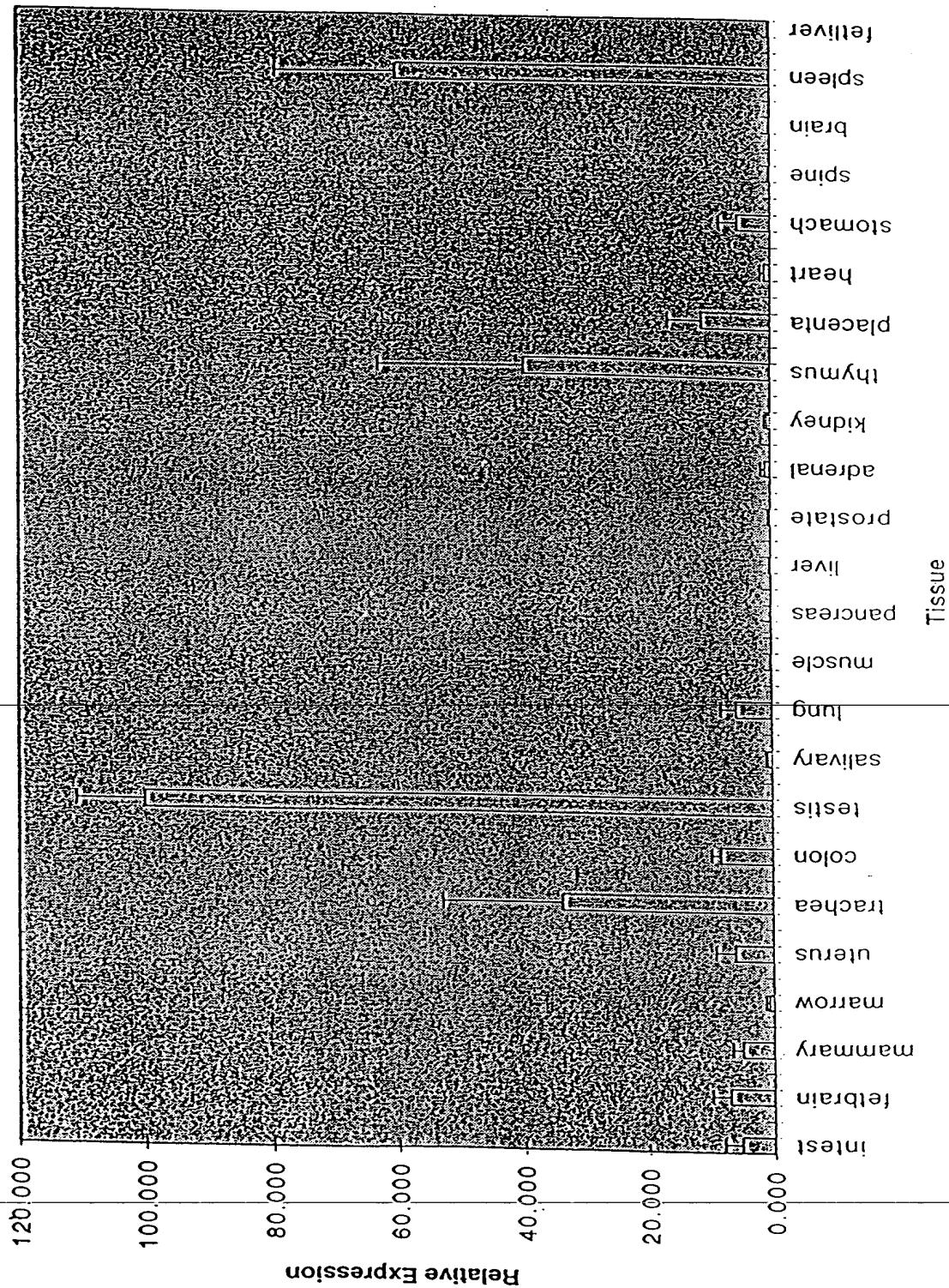
FIGURE 21**IL17C Distribution**

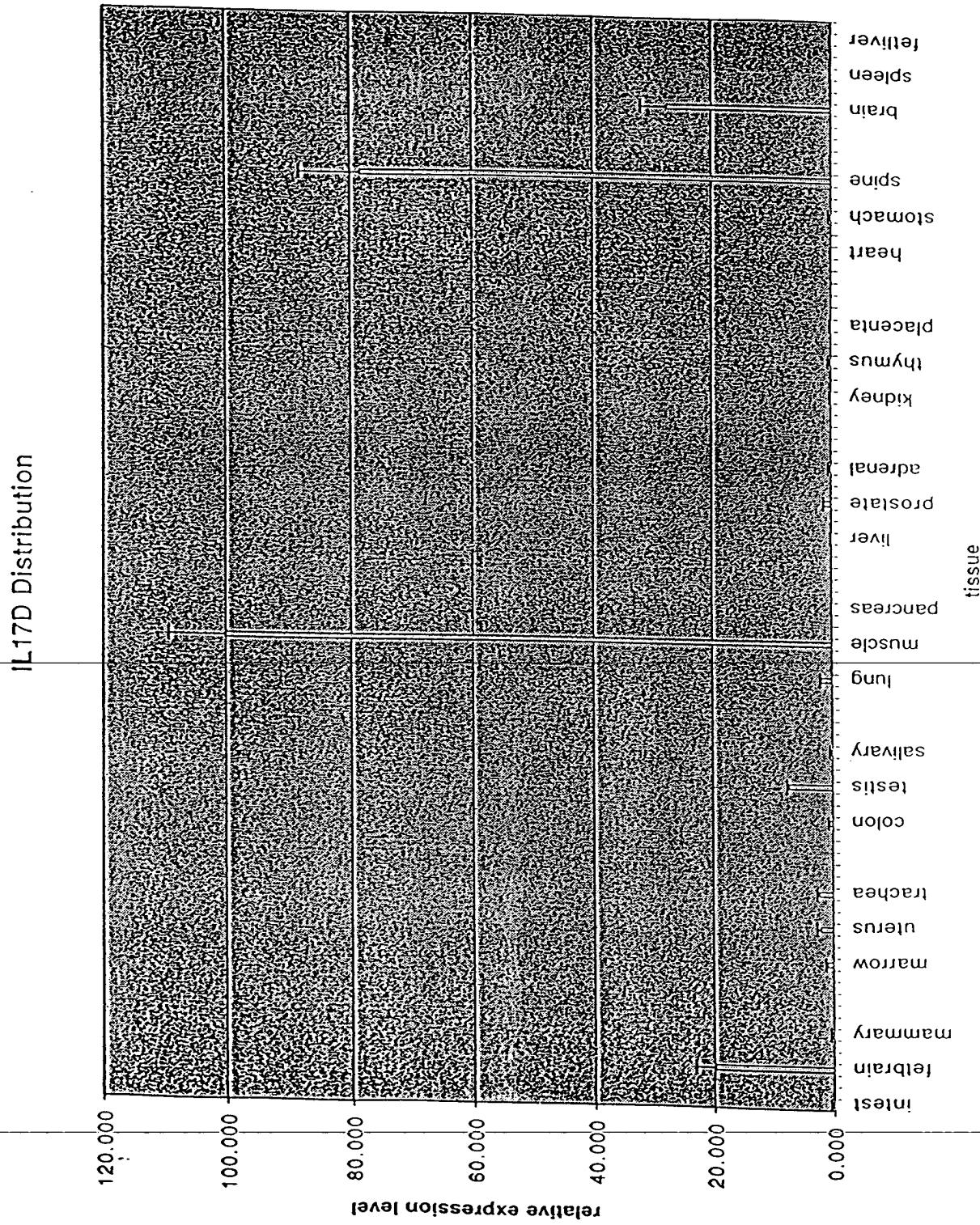
FIGURE 22

FIGURE 23

T E D T I F F O O D T

Brain	uterus
heart	fetal brain
kidney	fetal liver
liver	spinal chord
lung	placenta
colon	adrenal
marrow	pancreas
intestine	salivary
spleen	trachea
stomach	mammary
thymus	
prostate	
muscle	
testis	

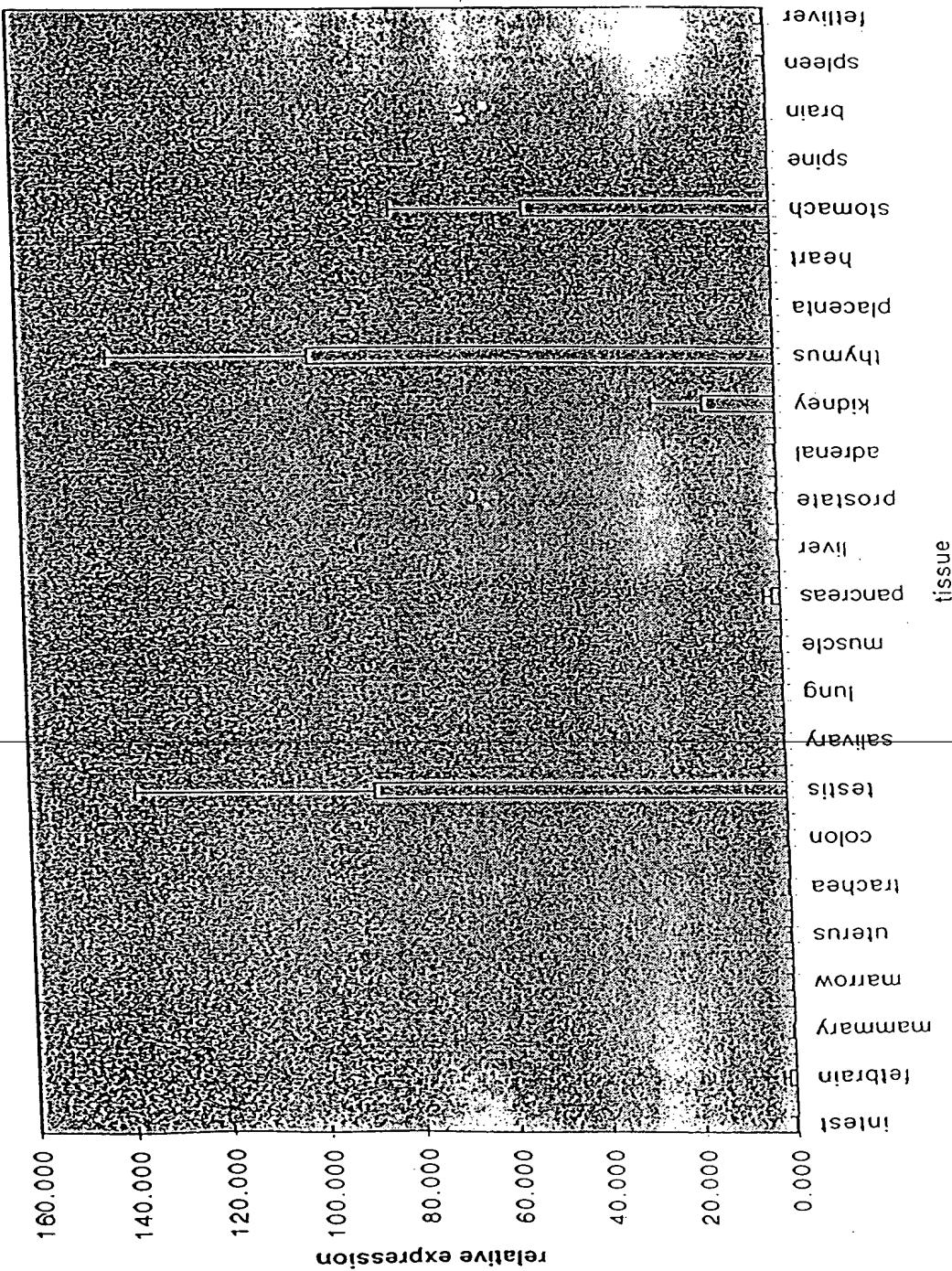
FIGURE 24**IL17 F Distribution**

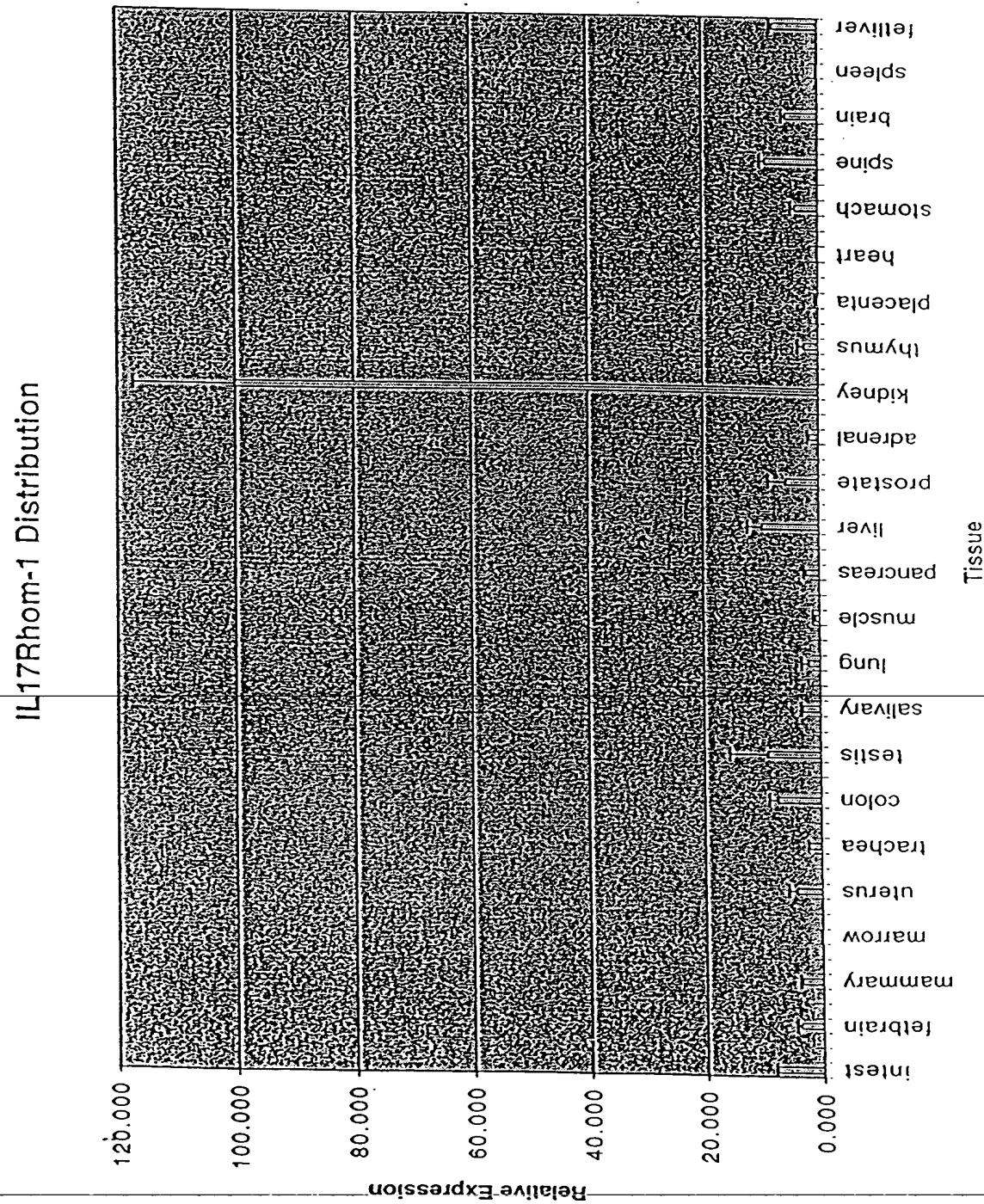
FIGURE 25

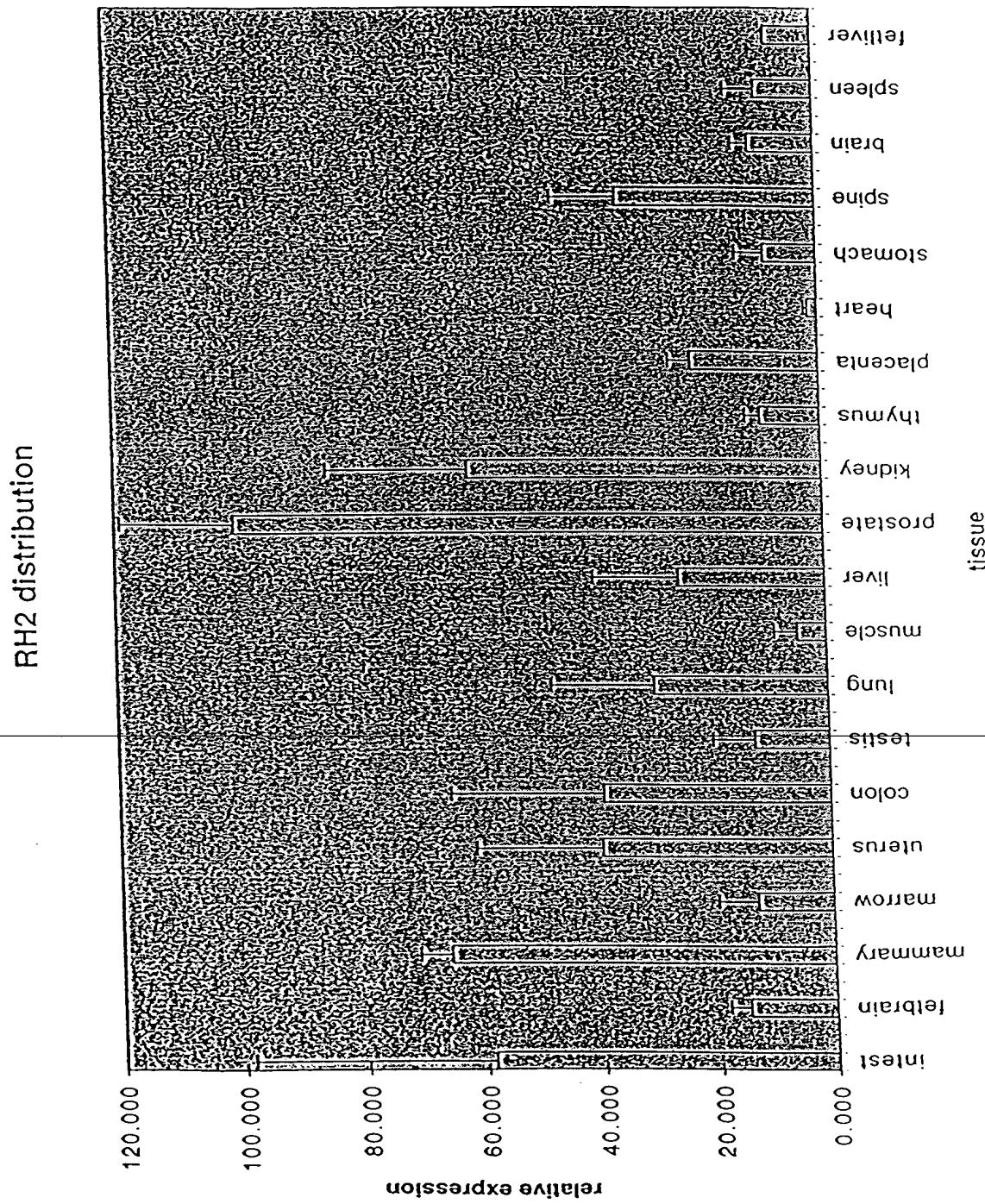
FIGURE 26

FIGURE 27

RH3 distribution

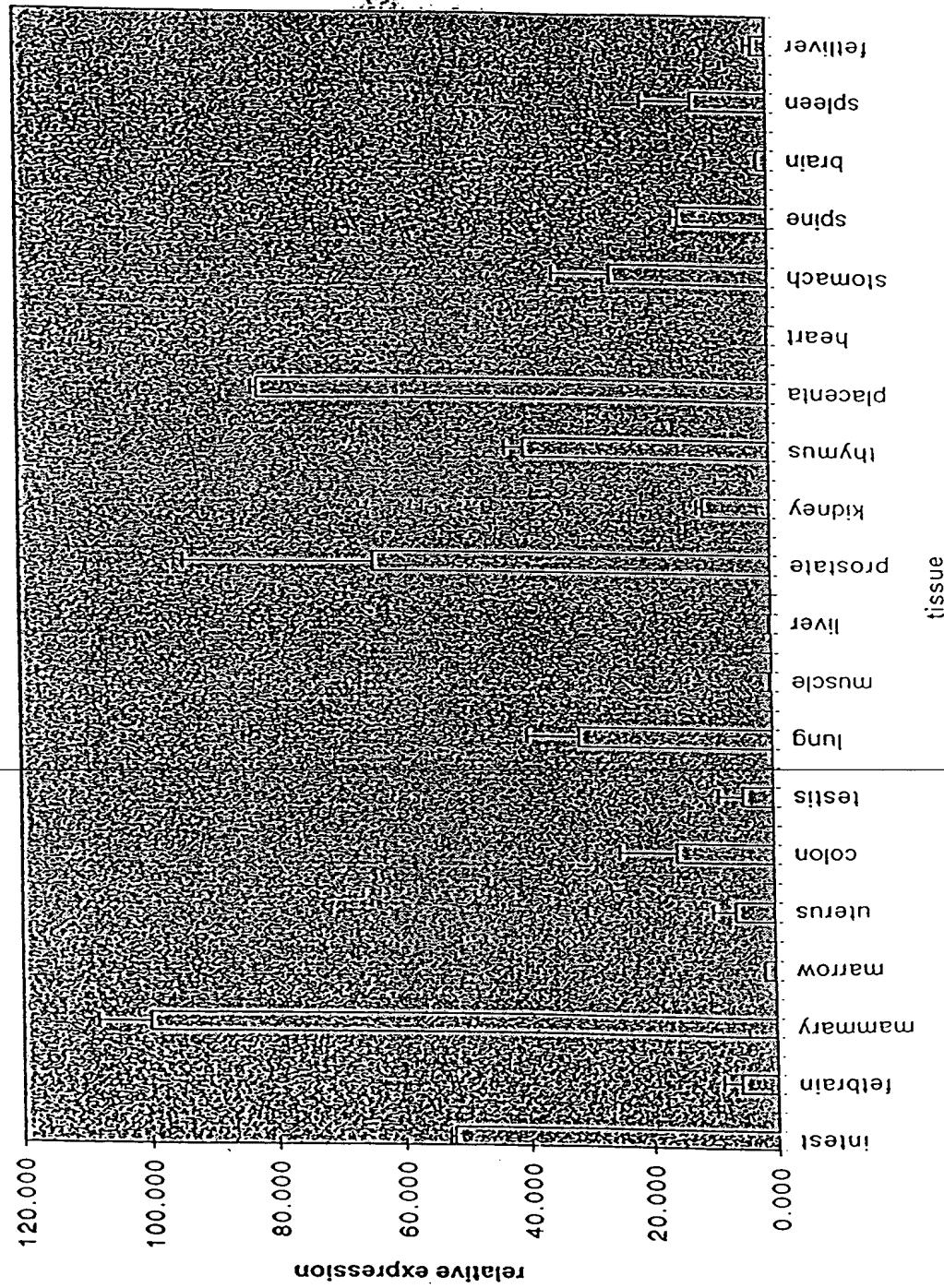


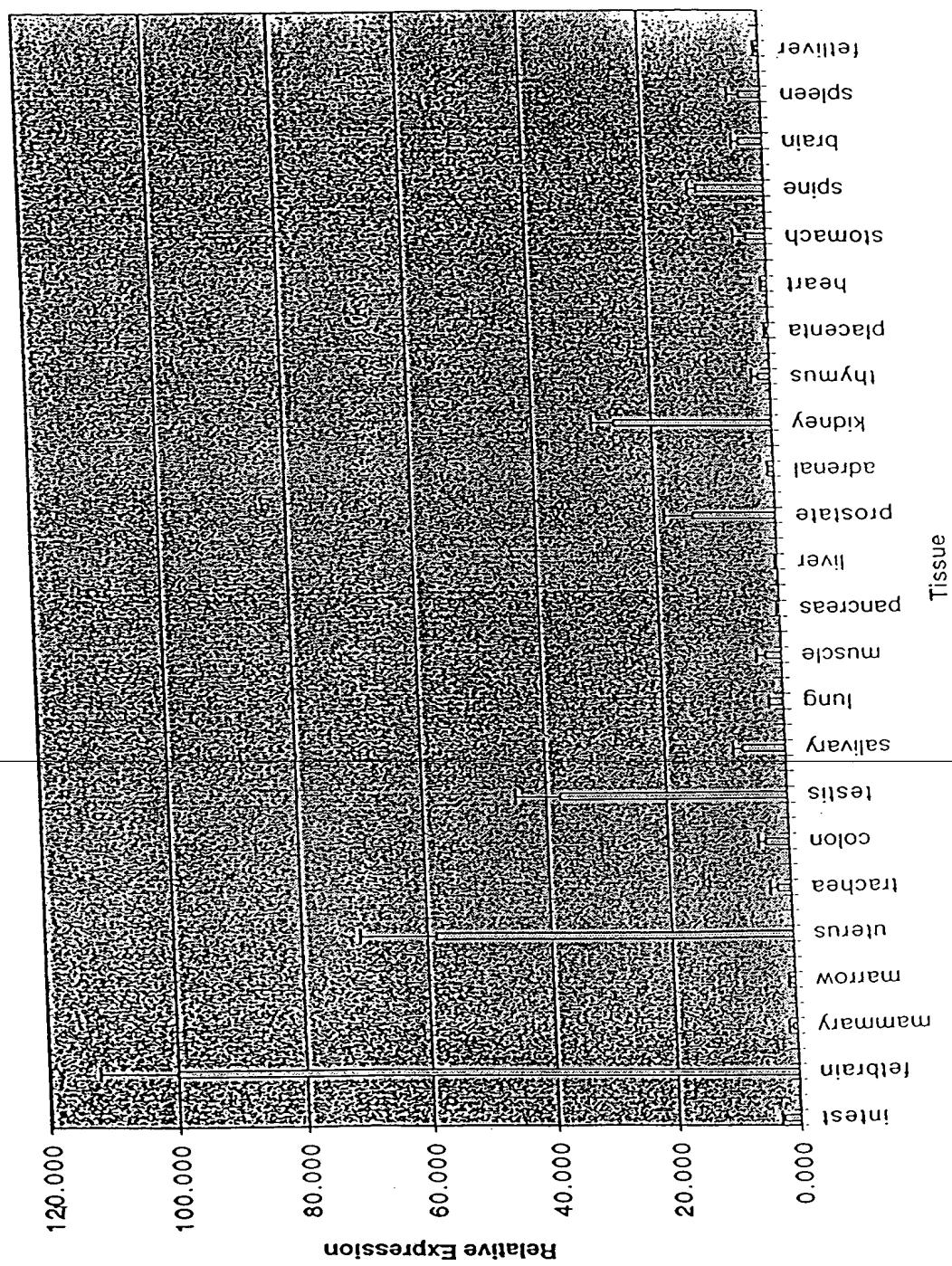
FIGURE 28**IL17 RH4 distribution**

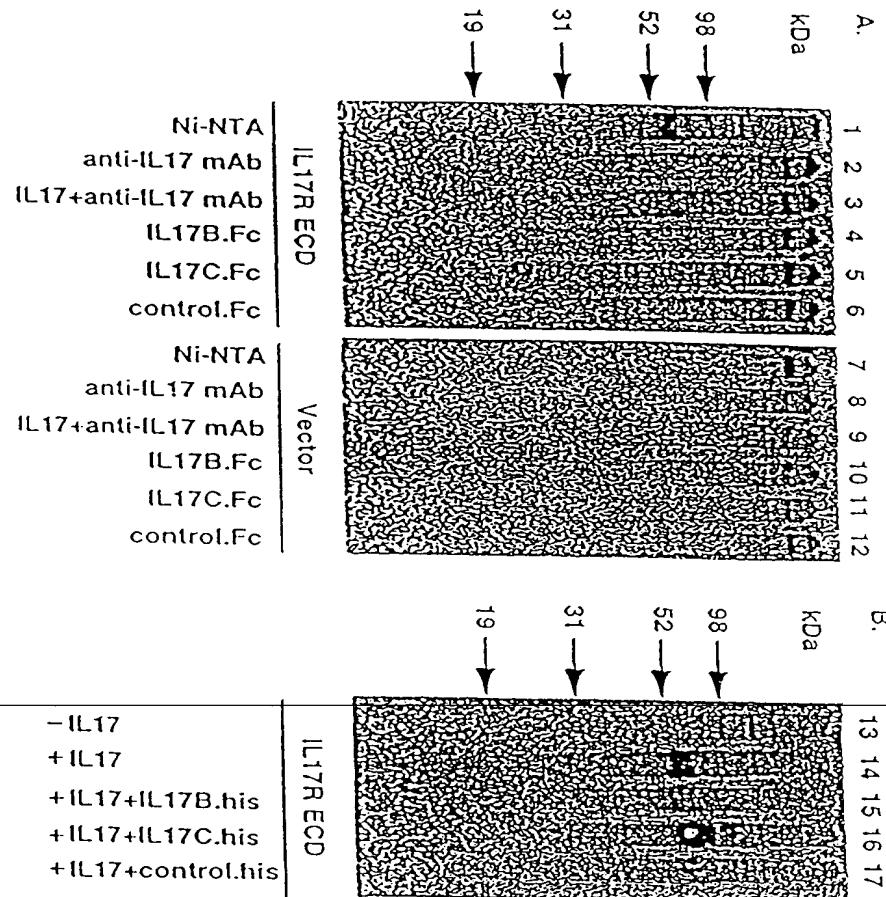
FIGURE 29

FIGURE 30

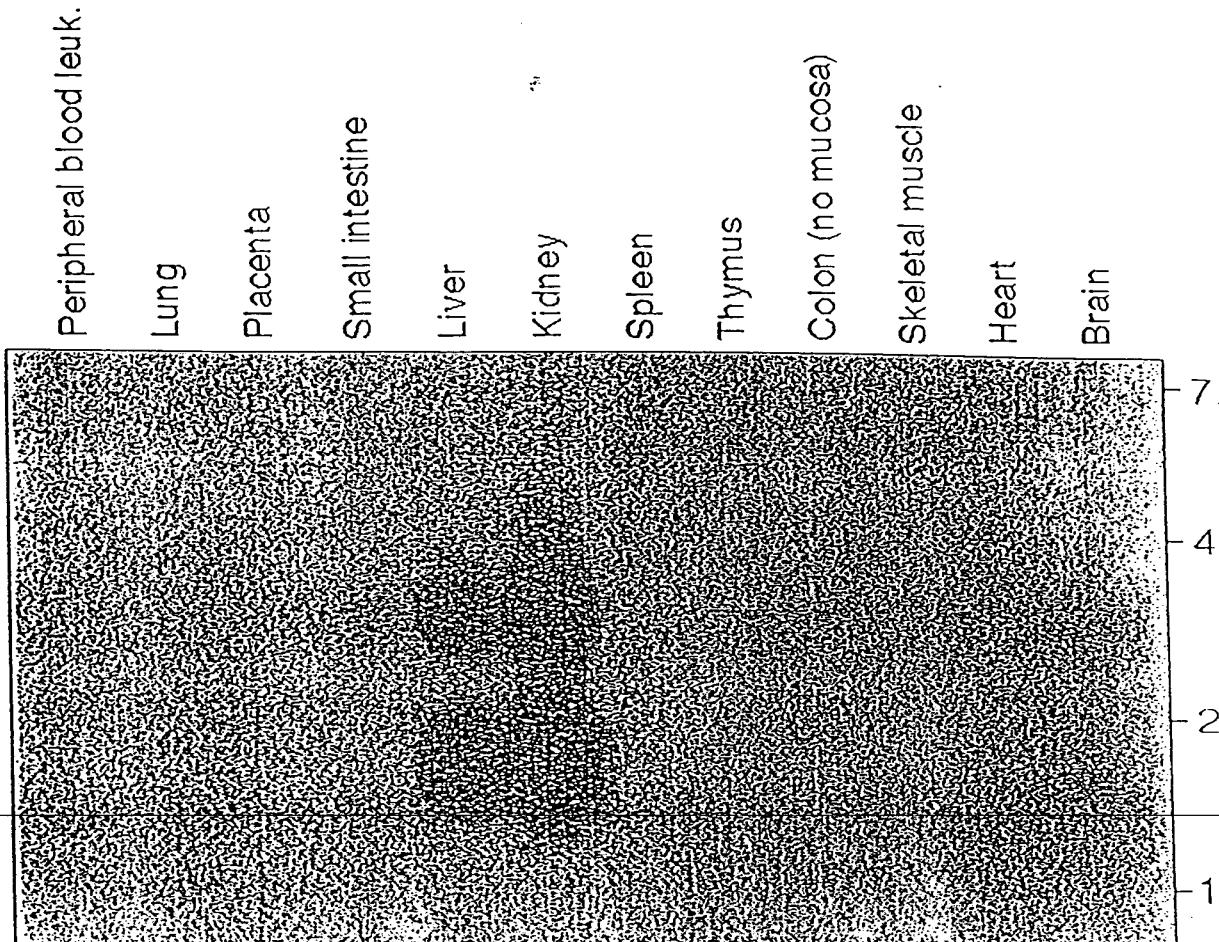
FIGURE 31A

FIGURE 31B

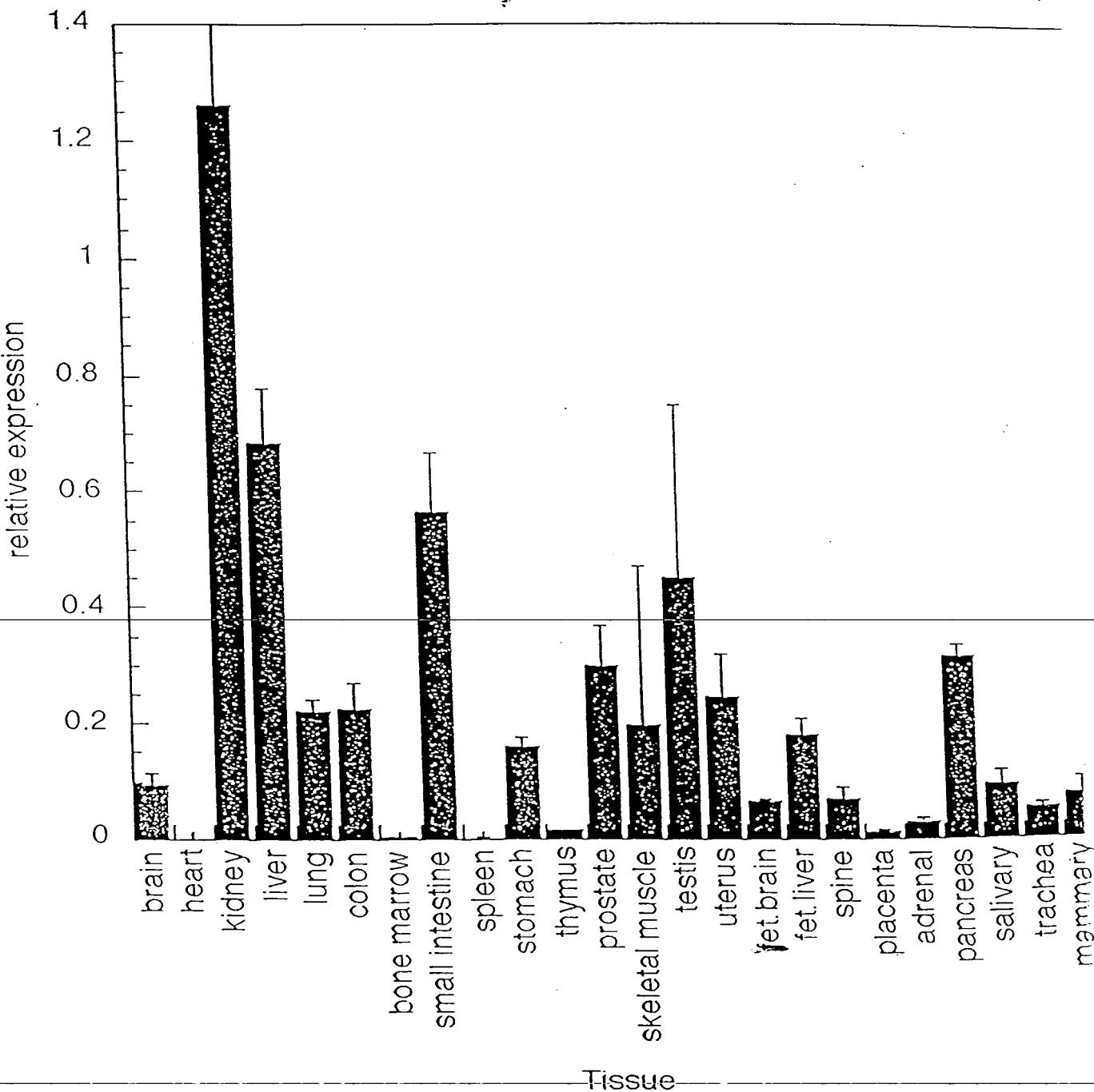


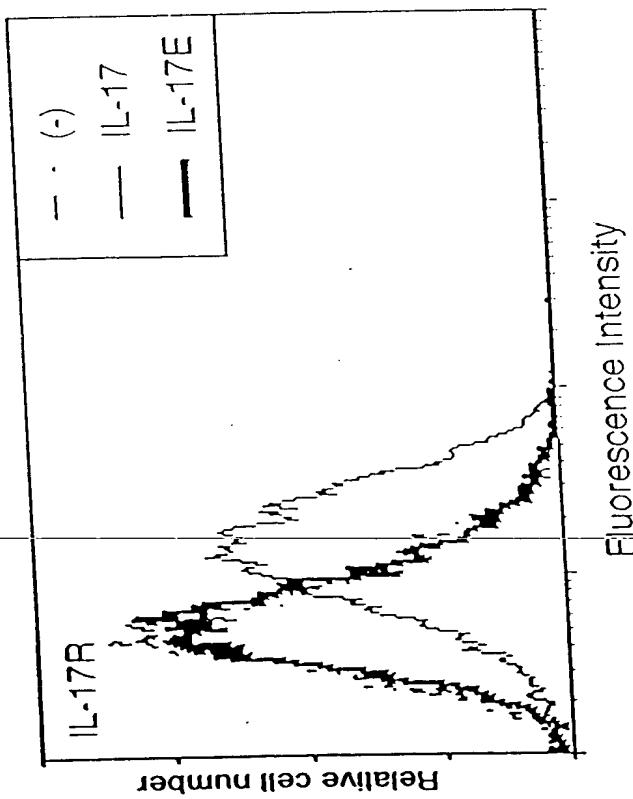
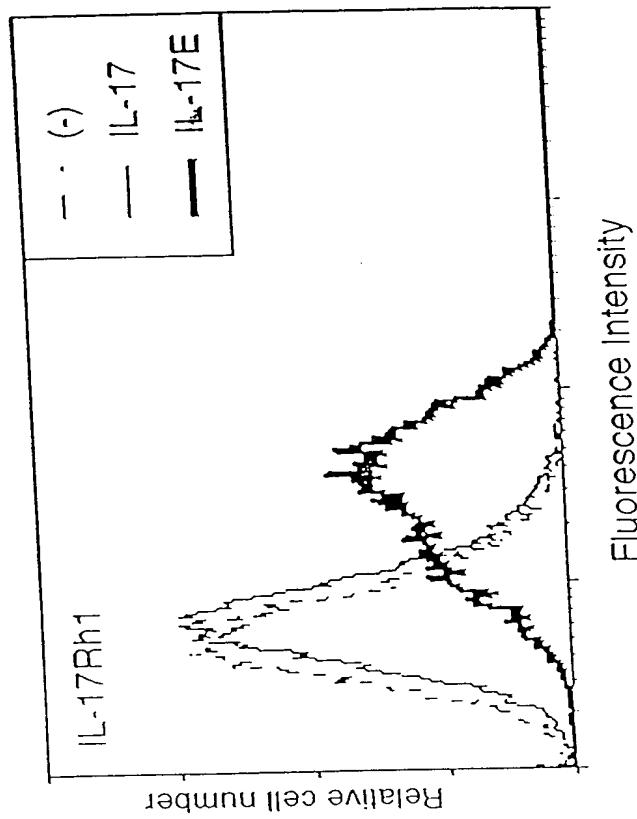
FIGURE 32A

FIGURE 32B

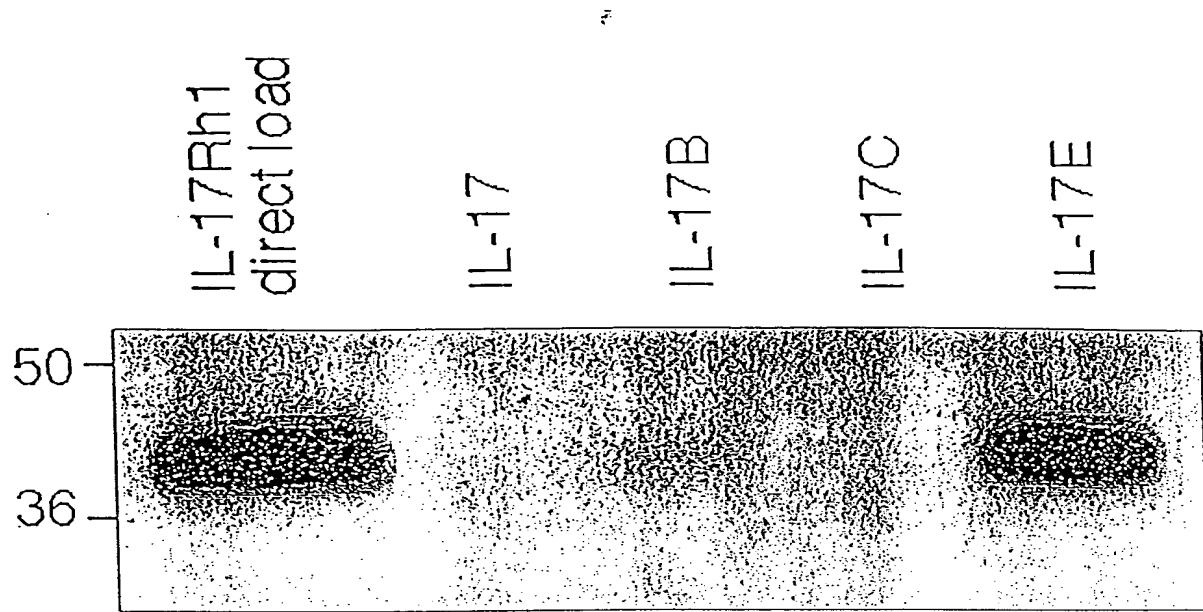


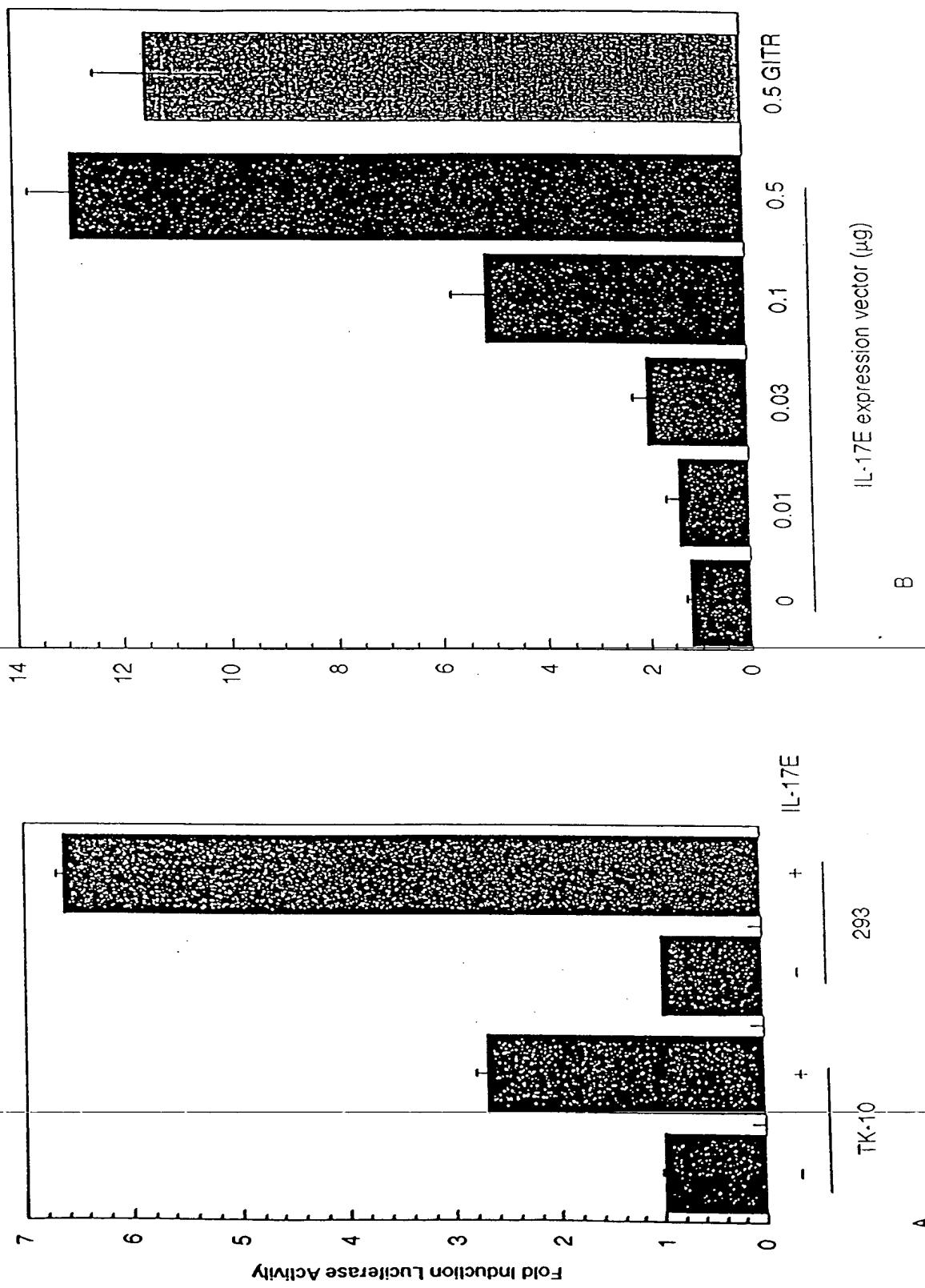
FIGURE 33

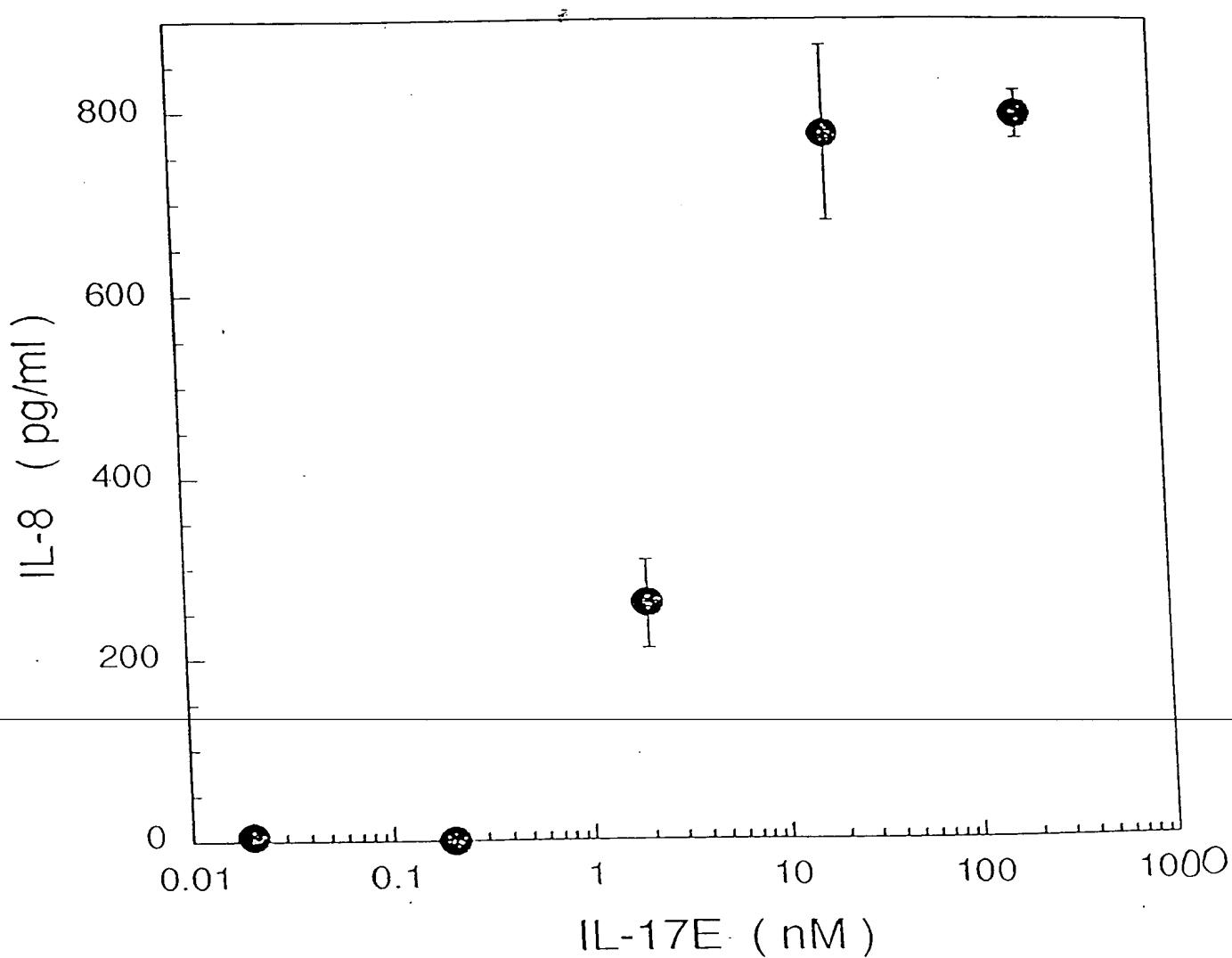
FIGURE 34

FIGURE 35

IL-17 family of cytokines has complex pattern
of overlapping receptor-ligand specificities

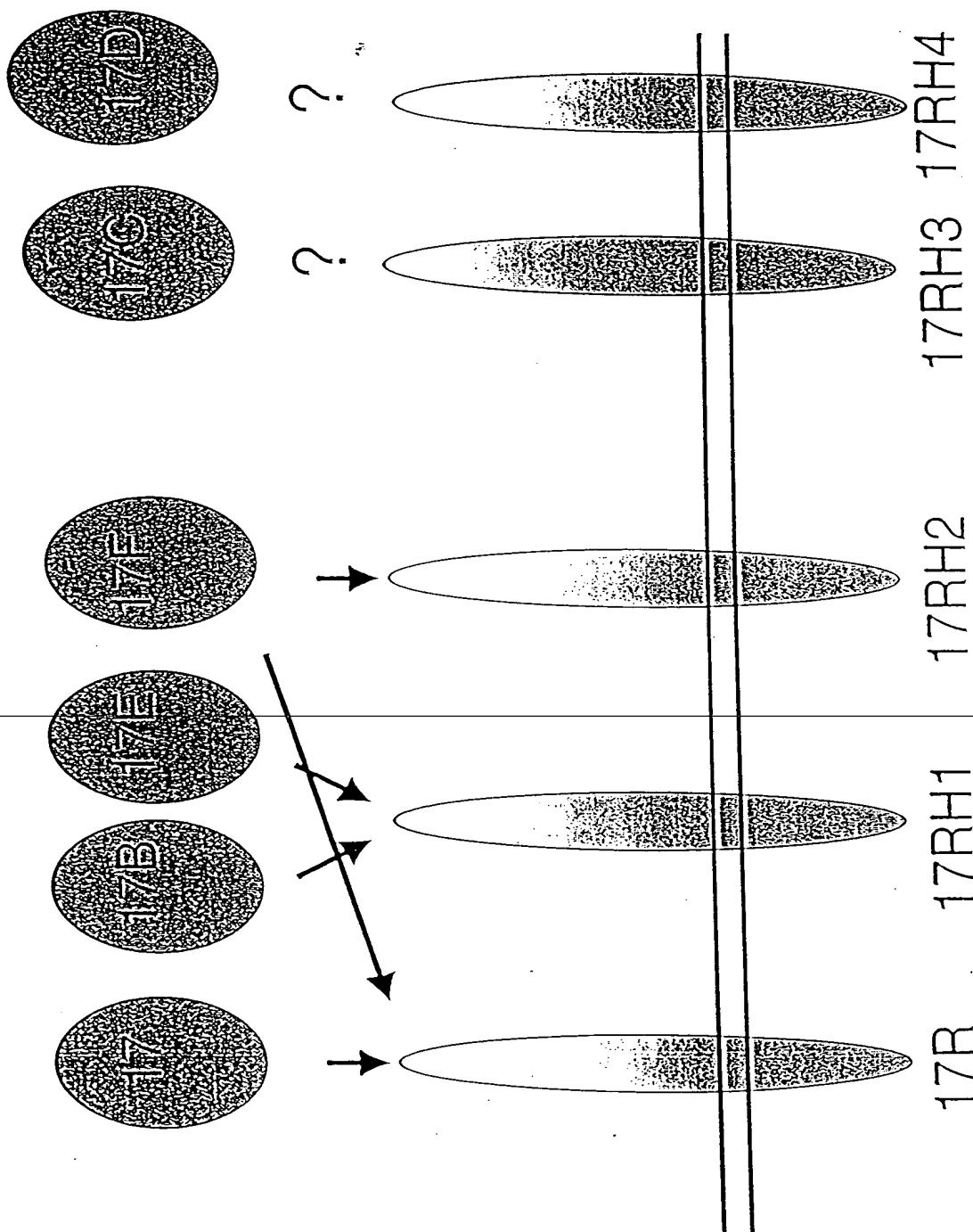
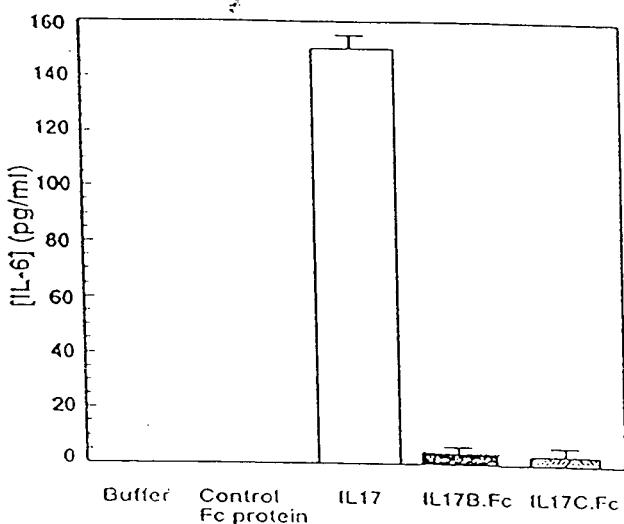
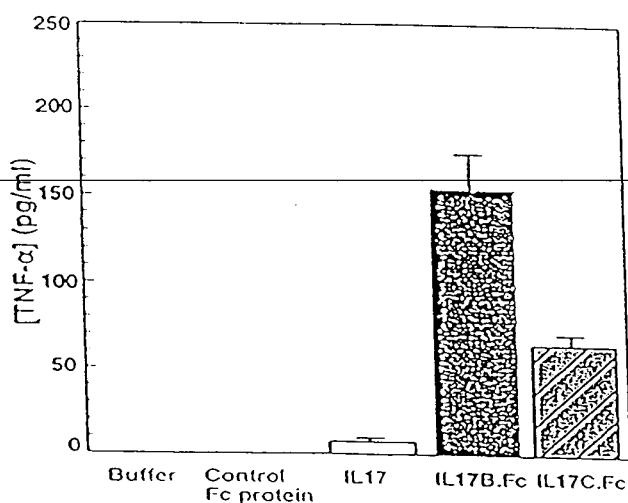


FIGURE 36**A. HFF cells****B. THP1 cells**

38/70 09157 - 103001

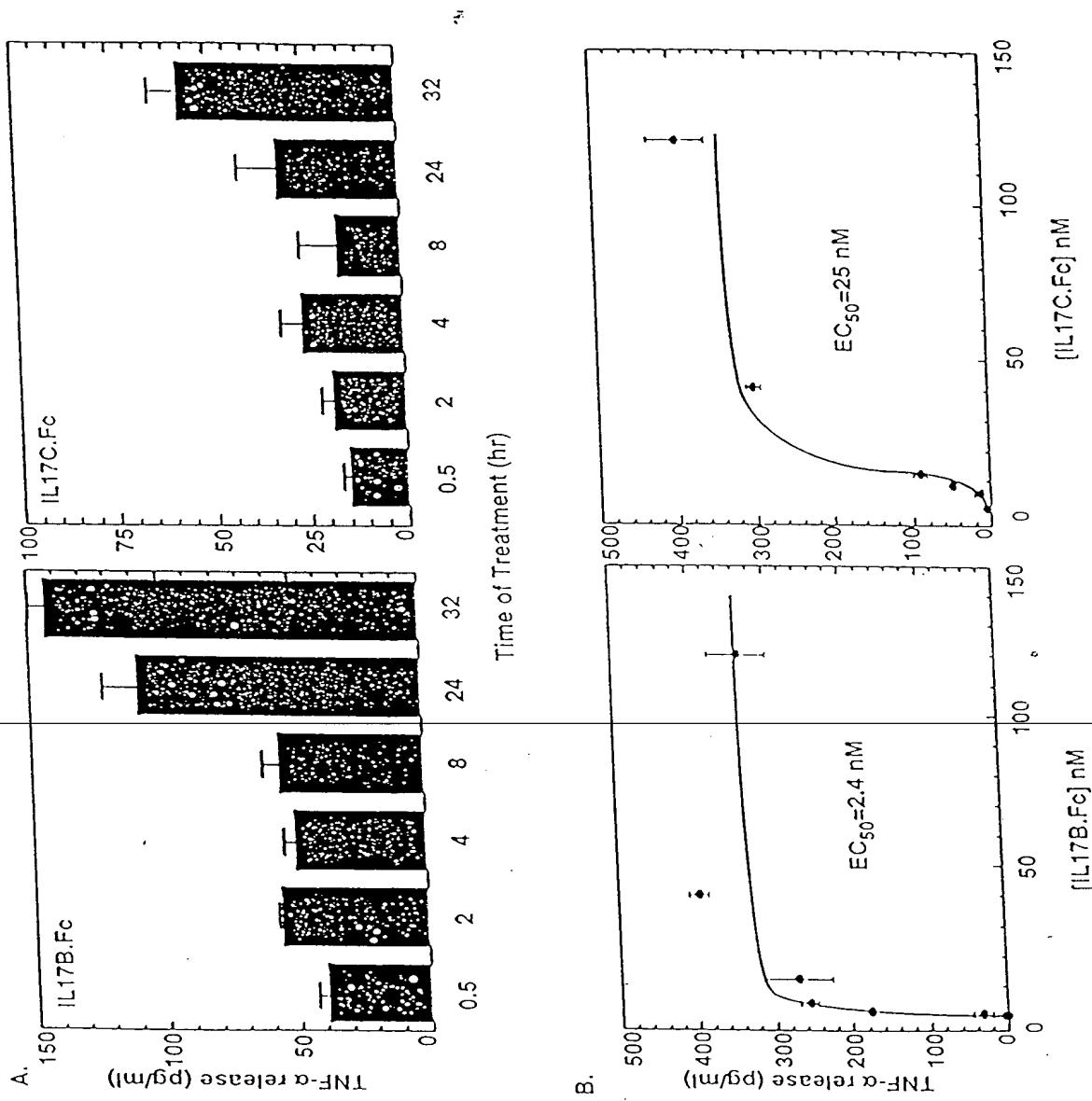
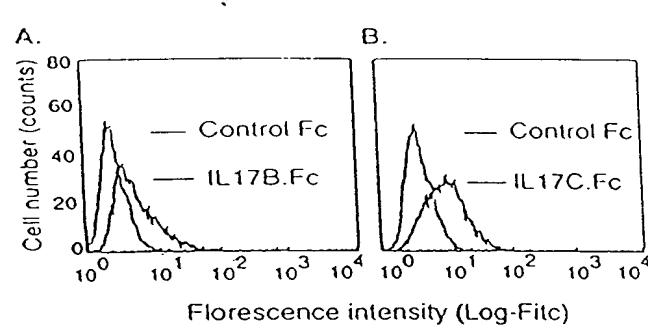
FIGURE 37

FIGURE 38

10000157-103003

FIGURE 39

IL-17 induces breakdown and inhibits synthesis of cartilage matrix

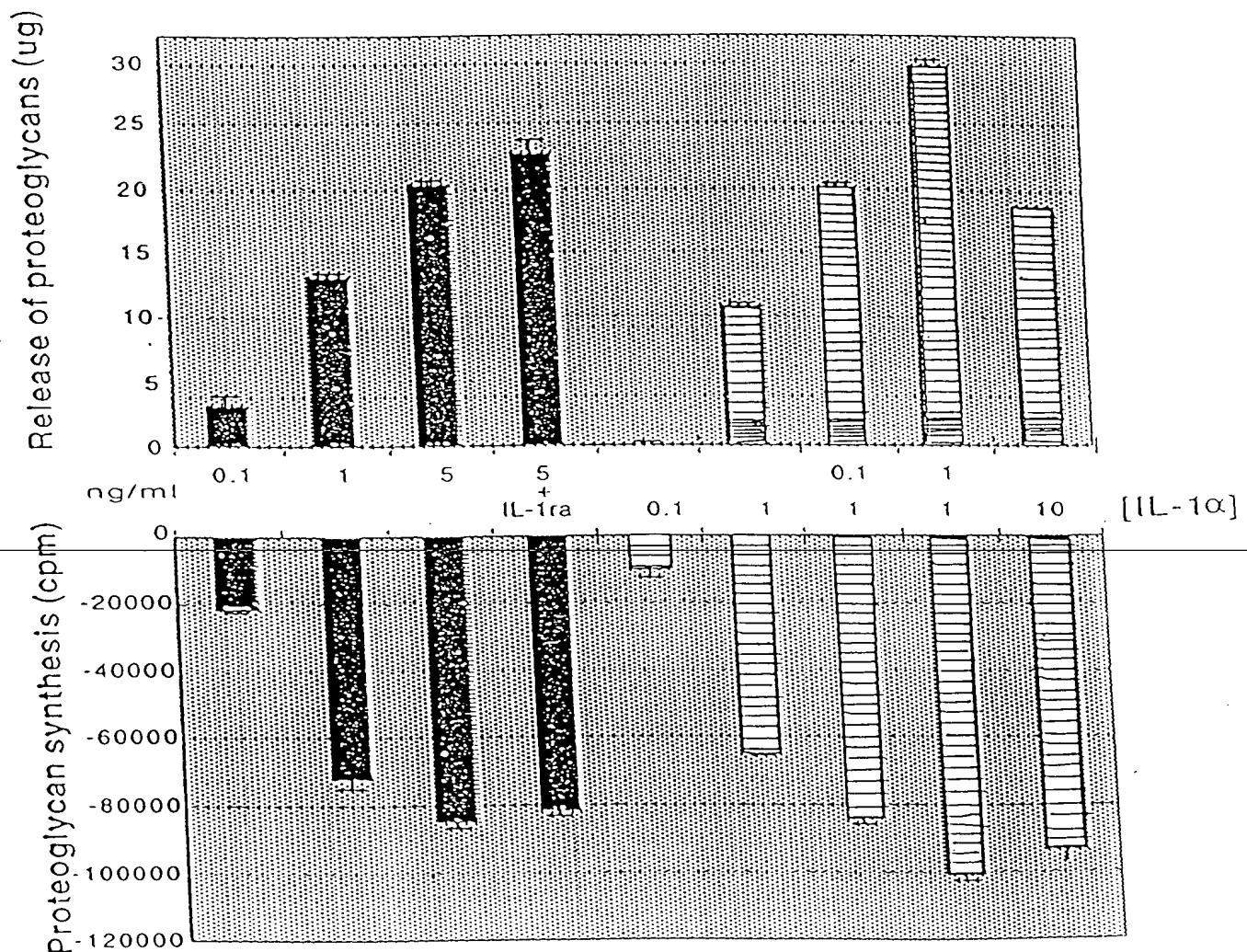


FIGURE 40

IL-17 increases basal and IL-1 α -induced nitric oxide release

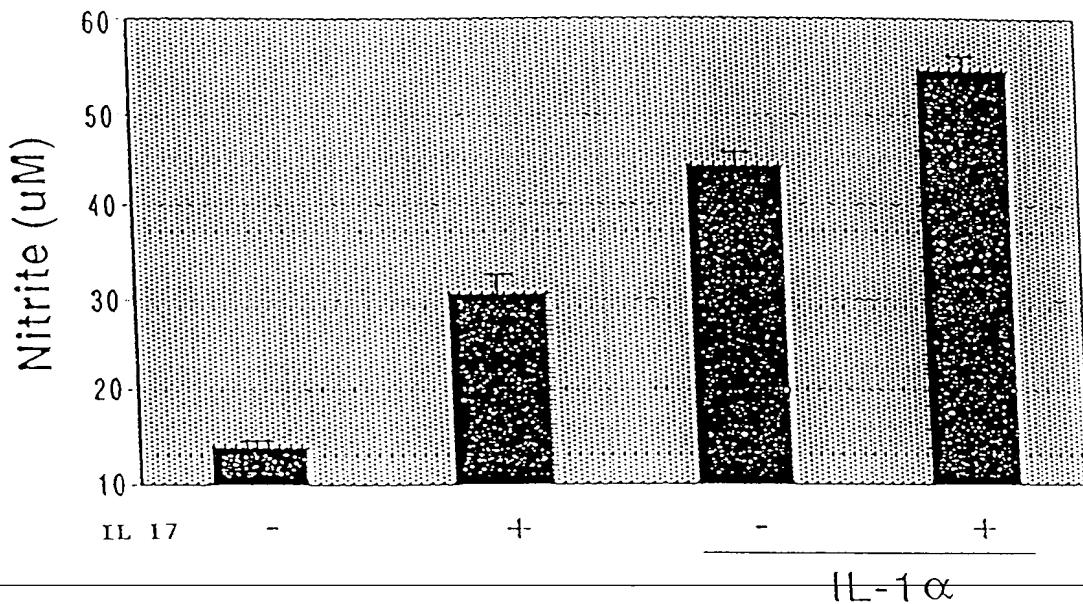
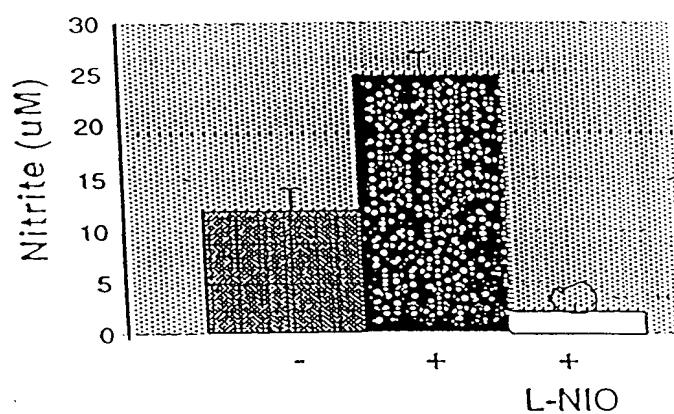


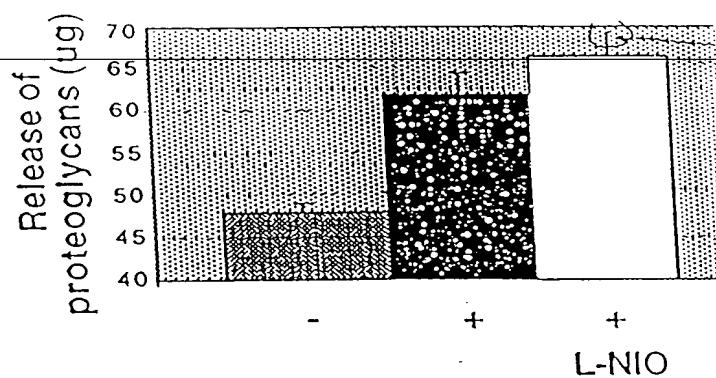
FIGURE 41

Inhibition of nitric oxide release does not block the detrimental effects of IL-17 on matrix breakdown or synthesis

A.



B.



C.

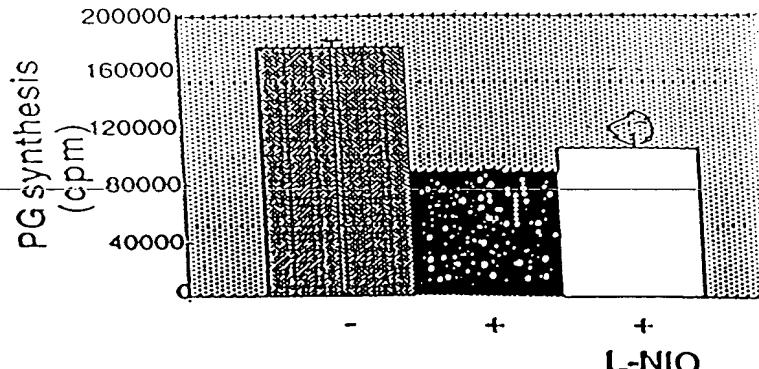


FIGURE 42

INHIBITION of NO release enhances
 IL-1 α -induced matrix breakdown
 but not matrix synthesis

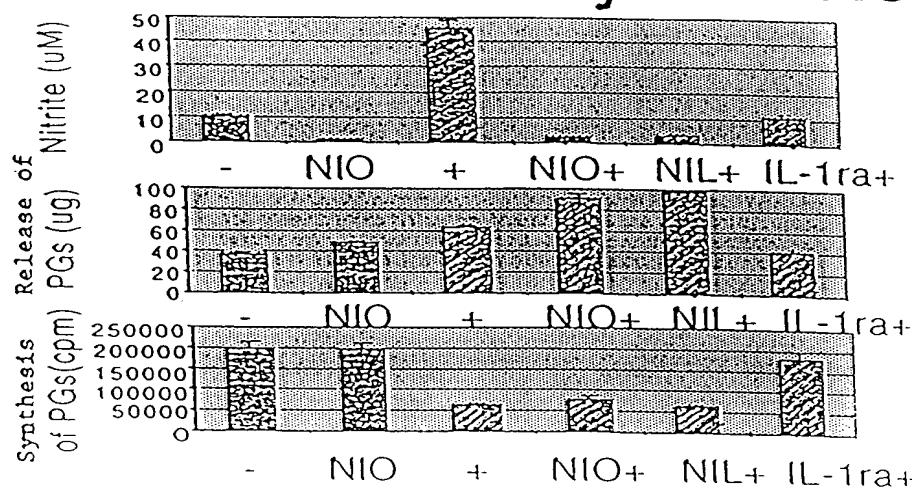


FIGURE 43

IL-17C

detrimental effects on articular cartilage

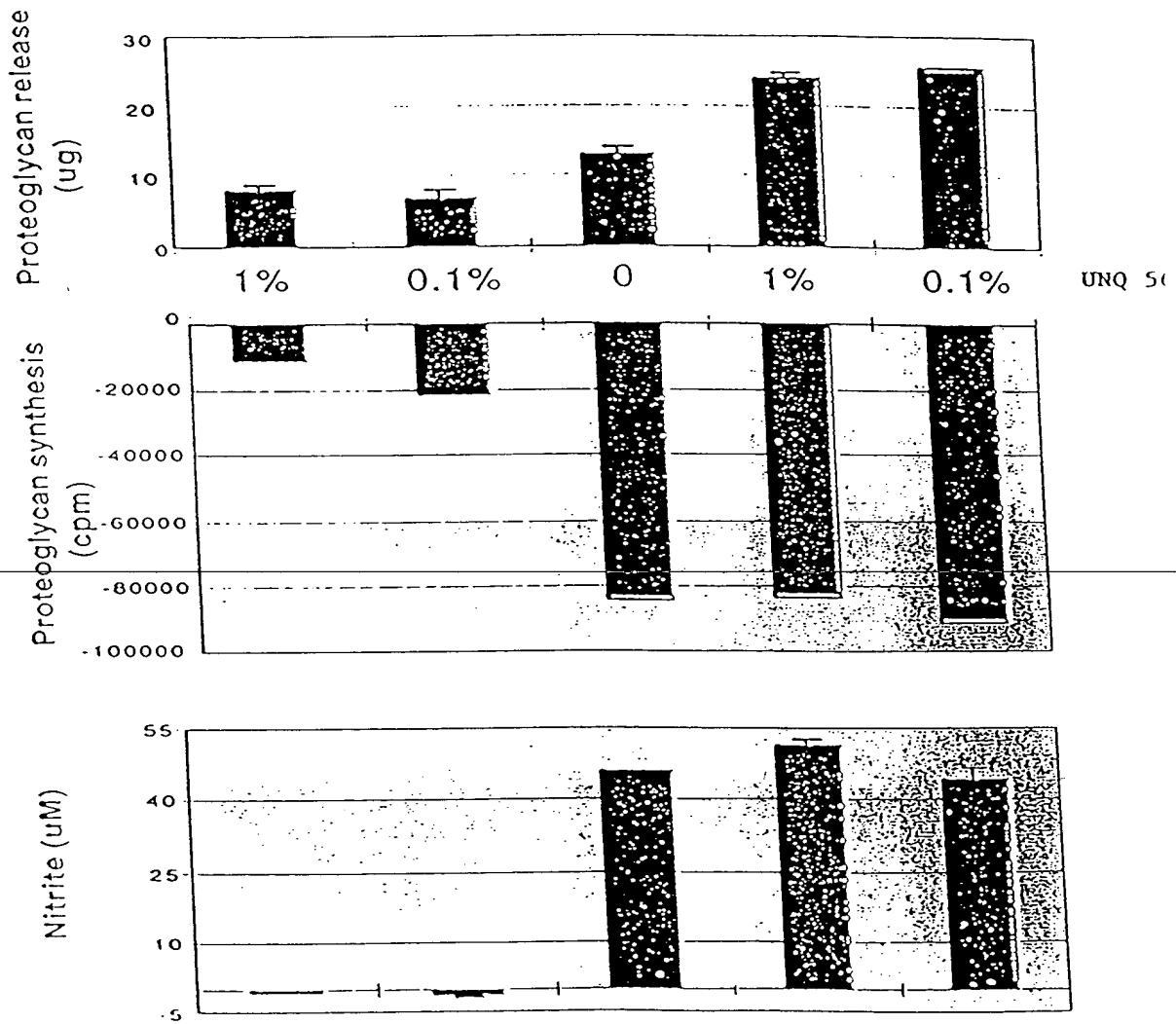
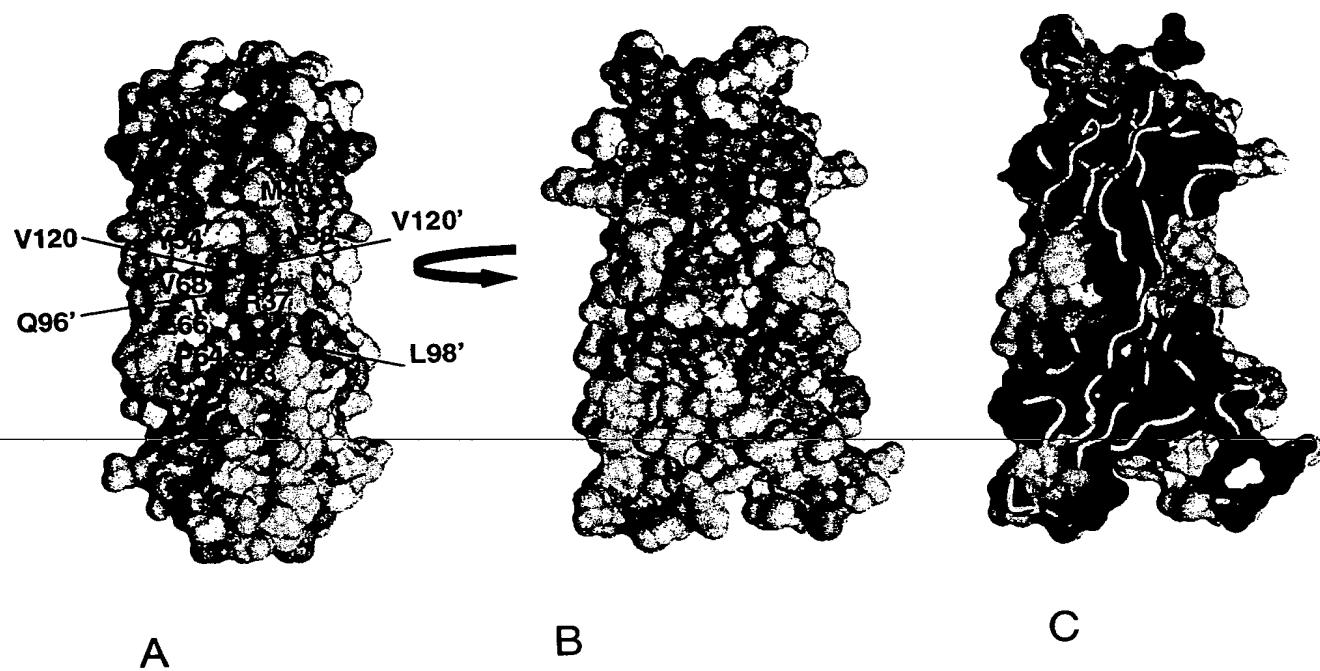
IL-1 α

FIGURE 51

10000157-103001

IL-17E is highly conserved between human and mouse

mlL-17E	1	----- - VAF FLAM IVG HT T V S L R I Q E G C S H L P S C C P S
mlL-17E	1	----- - M R E R P R G E D S S L I S L I S L ----- - YSH W P S C C P S
mlL-17E	35	----- - E Q E P P E W L K W S S A S V S P E P L S H T H A E S C R A S K D G P L N S R A I S P W S Y
mlL-17E	43	----- - R G G T S E L L R W S T V P V P L E P A R P N R H P E S C R A S E D G G P L N S R A I S P W R Y
mlL-17E	85	----- - E L D R D L N R V P Q D L Y H A R C L C P H C V S L Q T G S H M D P L G N S V P L Y H N Q T V F Y R
mlL-17E	93	----- - E L D R D L N R L P Q D L Y H A R C L C P H C V S L Q T G S H M D P R G N S E L Y H N Q T V F Y R
mlL-17E	135	----- - R P U H G E E G T H R R R Y C L E R R L Y V S L A C V C V R P R V M A
mlL-17E	143	----- - R P C H G E K G T H K G Y C L R R L Y V S L A C V C V R P R V M G

FIGURE 53

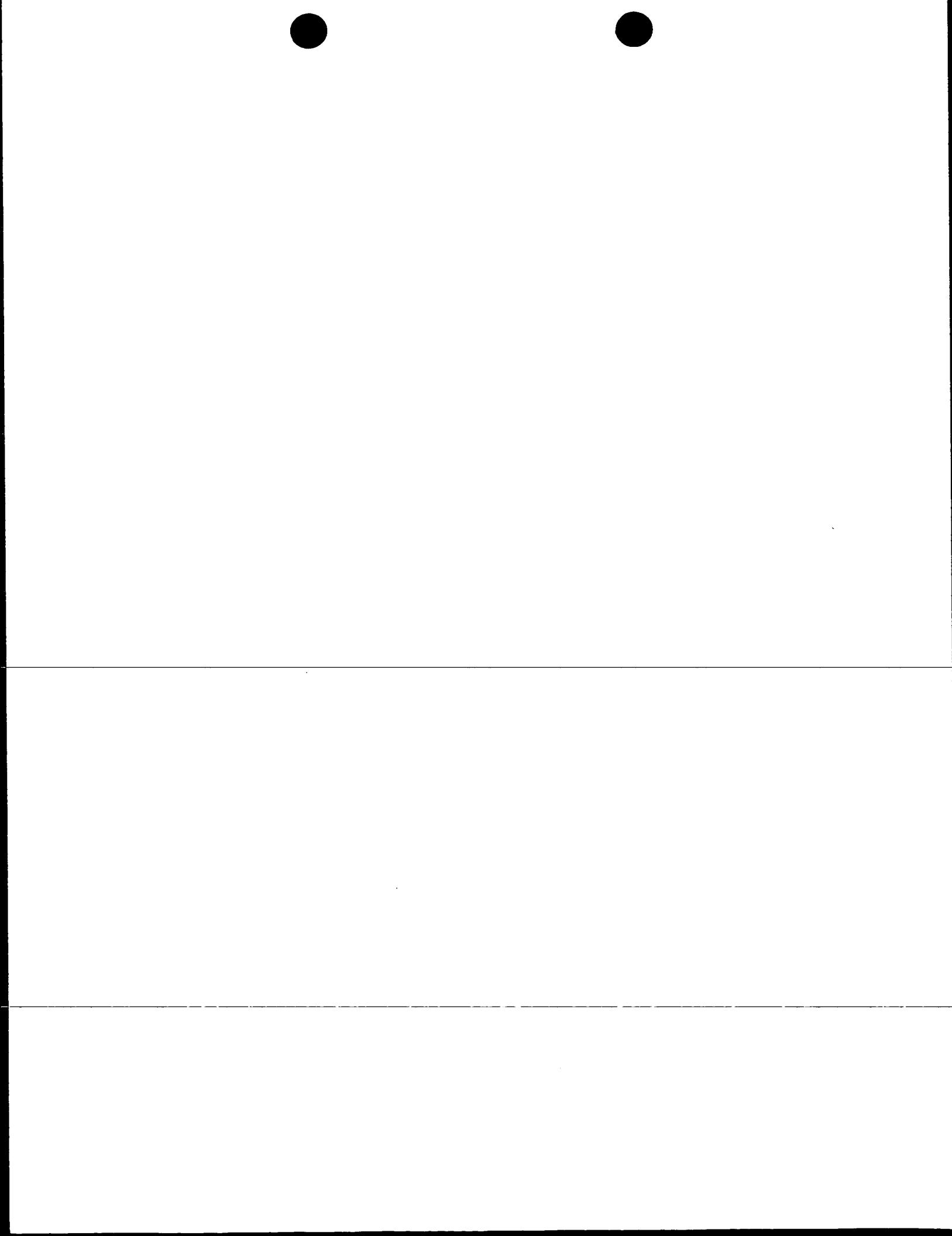


FIGURE 8

MLVAGFLLALPPSWAAGAPRAGRRPARPRGCADRPEELLEQLYGRLAAGVLSAFHHTLQLGPREQARNASC
PAGGRPGDRRFRPPTNLRSPWAYRISYDPARYPRYLPEAYCLCRGCLTGLFGEEDVFRSAPVYMPPTVV
LRRTPACAGGRSVYTEAYVTIPVGCTCVPPEKDADSINSSIDKQGAKLLLGPNDAPAGP

Signal peptide: Amino acids 1-15

N-glycosylation sites: Amino acids 68-72;181-185

Tyrosine kinase phosphorylation site: Amino acids 97-106

N-myristoylation sites: Amino acids 17-23;49-55;74-80;
118-124

Amidation site: Amino acids 21-25

4.0000157-4030034

FIGURE 4

MTLLPGLLFLTWLHTCLAHHDPSLRGHPHSGTPHCYSAEELPLGQAPPILLARGAKWGQALPVALVSSLE
AASHRGRHERPSATTQCPVLRPEEVLEADTHQRSISPWRYRVDTDEDRYPQKLAFAECLRGCIDARTGRE
TAALNSVRLLQSLLVLRRLRPCSRDGSGLPTPGAFAFHTEFIHVPVGCTCVLPRSV

Signal peptide: Amino acids 1-18
Tyrosine kinase phosphorylation site: Amino acids 112-121
N-myristoylation sites: Amino acids
32-38;55-61;133-139
Leucine zipper pattern: Amino acids 3-25
Homologous region to IL-17: Amino acids 99-195

1000157-1038064

FIGURE 6

MRERPRLGEDSSLISLFLQVVAFLAMVMGHTHTYSHWPSCCPKGQDTSEELLRWSTVPVPPLEPARPNRHP
ESCRASEDGPLNSRAISPWRYELDRDLNRLPQDLYHARCLCPHCVSLQTGSHMDPRGNSELLYHNQTVFYR
RPCHGEKGTHKGYCLERRLYRVSLACVCVRPRVMG

Signal peptide: Amino acids 1-32

N-glycosylation site: Amino acids 136-140

Tyrosine kinase phosphorylation site: Amino acids 127-135

N-myristoylation sites: Amino acids 44-50;150-156

N-myristoylation sites: Amino acids 44-50;150-156

FIGURE 7

ATGCTGGTAGCCGGCTTCCTGCTGGCGCTGCCGCCGAGCTGGCCGGCGCCCCAGGGCGGGCAGGCG
CCCCCGCGGGCCCGGGGCTGCGCGGACCGGCCGGAGGAGCTACTGGAGCAGCTGTACGGCGCCTGGCG
CCGGCGTCTAGTCGCTTCCACCACACGCTGCAGCTGGGCCGGTGAAGCAGGCCGAAACGCGAGCTGC
CCGGCAGGGGGCAGGCCCGCGACCGCCGCTCCGCCGCCACCAACCTGCGCAGCGTGTGCCCTGGC
CTACAGAATCTCCTACGACCCGGCAGGTACCCAGGTACCTGCCTGAAGCCTACTGCCTGTGCCGGGCT
GCCTGACCGGGCTGTTCGGCGAGGAGGACGTGCGCTCCGCAGGCCCTGTCTACATGCCAACGTCGTC
CTGCGCCGCACCCCGCCTGCGCCGGCGTCCGTCTACACCGAGGCCTACGTACCATCCCCGTGG
CTGCACCTGCGTCCCCGAGCCGGAGAAGGACGCAGACAGCATCAACTCCAGCATGACAAACAGGGCGCA
AGCTCCTGCTGGCCCCAACGACGCGCCCGCTGGCCCTGAGGCCGGTCTGCCCGGGAGGTCTCCCCGG
CCCGCATCCCAGGGCGCCAAGCTGGAGCCGCTGGAGGGCTCGGTGGCGACCTCTGAAGAGAGTCACC
GAGCAAACCAAGTGCCGGAGCACCAGCGCCGCTTCCATGGAGACTCGTAAGCAGCTCATCTGACACGG
GCATCCCTGGCTTGCTTTAGCTACAAGCAAGCAGCGTGGCTGAAAGCTGATGGAAACGACCCGGCACGG
GCATCCTGTGTGCGGCCCGCATGGAGGGTTGGAAAAGTCACGGAGGCTCCCTGAGGAGCCTCTCAGATC
GGCTGCTGCGGGTGCAGGGCGTGAECTACCGCTGGGTGCTTGCAAAGAGATAGGGACGCATATGCTTTT
AAAGCAATCTAAAATAATAAGTATAGCGACTATACCTACTTTAAAATCAACTGTTGAATAGA
GGCAGAGCTATTTATATTCAAATGAGAGCTACTCTGTTACATTCTAACATATAACATGTTTT
ACTTCTCTGGTAGAATTTAAAGCATAATTGGAATCCTTGGATAAAATTGTTAGCTGGTACACTCTGG
CCTGGGTCTCTGAATTCAAGCTGTCAACCGATGGCTGACTGATGAAATGGACACGTCTCATCTGACCCACTC
TTCCTCCACTGAAGGTCTCACGGGCCTCCAGGTGGACCAAAGGGATGCACAGGGCGCTCGCATGCCCA
GGGCCAGCTAAGAGTTCCAAAGATCTCAGATTGGTTAGTCATGAATAACATAAACAGTCTCAAACCTCGC
ACAATTTTCCCCCTTGAAAGCCACTGGGCCAATTGTGGTTAAGAGGTGGTGAAGATAAGAAGTGG
ACGTGACATCTTGCCAGTTGTCAGAAGAATCCAAGCAGGTATTGGCTTAGTTGTAAGGGCTTCTGTTCTGCA
GGCTGAATATGAGGACAAAGTGGCACGTTAGCATCTGCAGAGATCAATCTGGAGGCTCTGTTCTGCA
TTCTGCCACGAGAGCTAGGTCTTGATCTTCTTAGATTGAAAGTCTGTCTGAACACAATTATTGT
AAAAGTTAGTTAGTTCTTTAAATCATTAAAGAGGCTTGCTGAAGGAT

Inflammatory Bowel Disease: Expression of IL-17 Family in Mouse Model of IBD

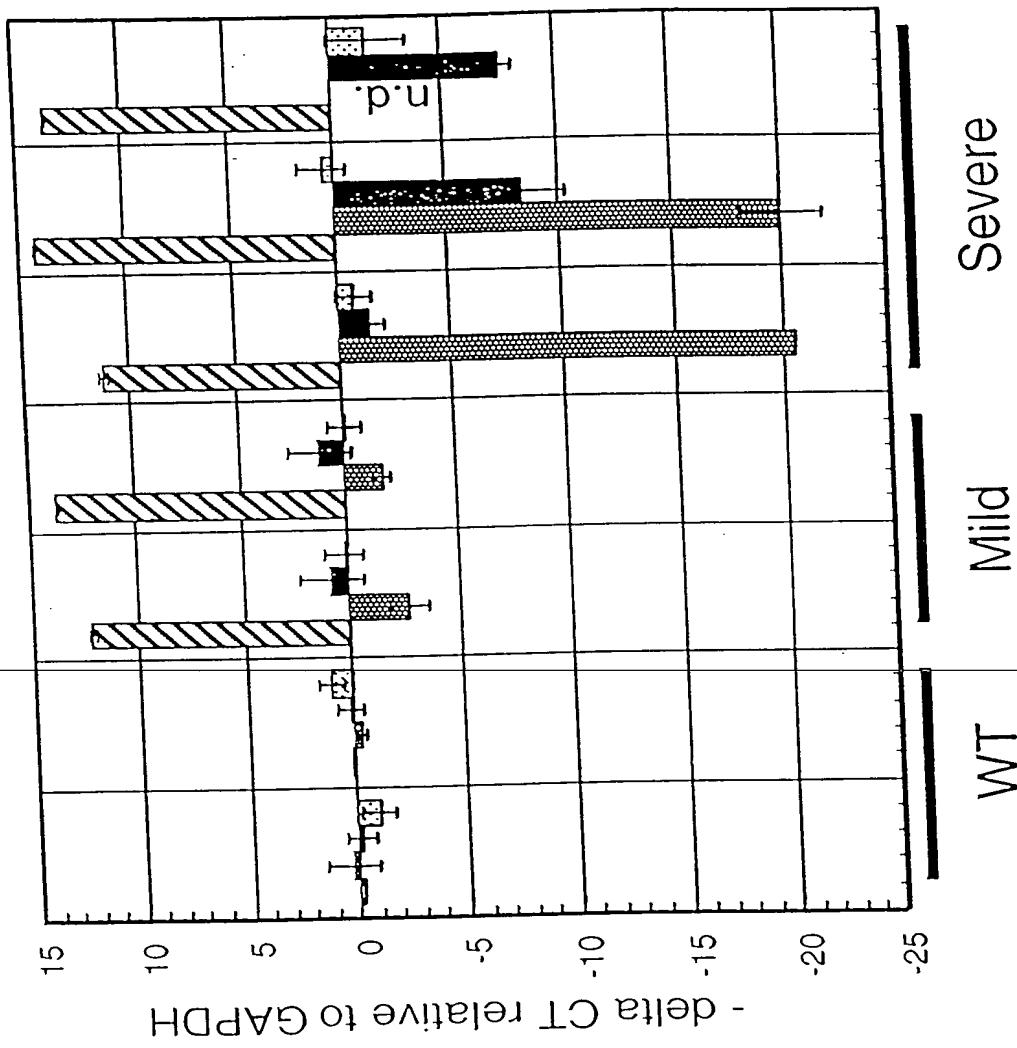


FIGURE 4A

TOURET TM / ESTROFOL 1000000

IL-17D, present in brain, decreases rapidly following stroke

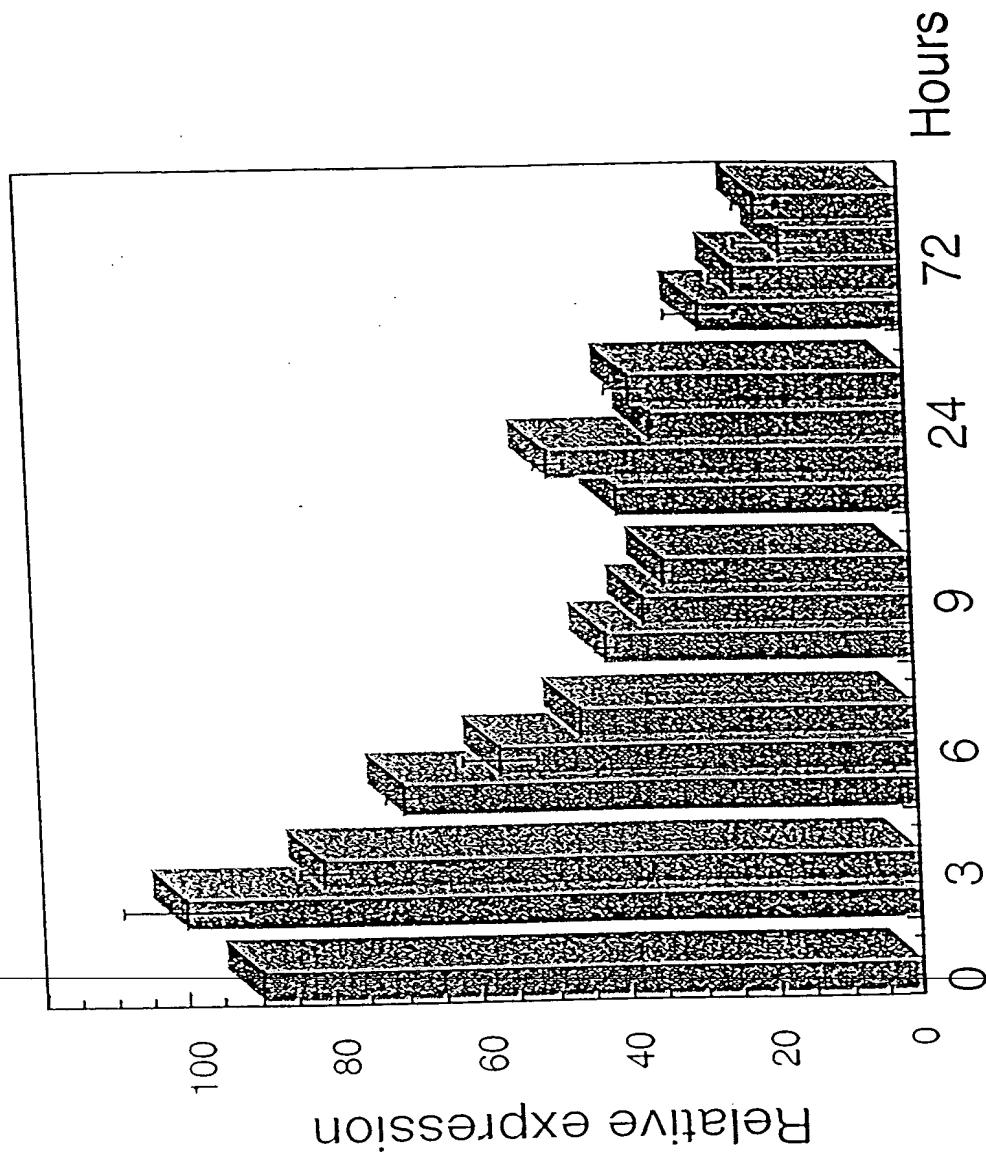


FIGURE 45

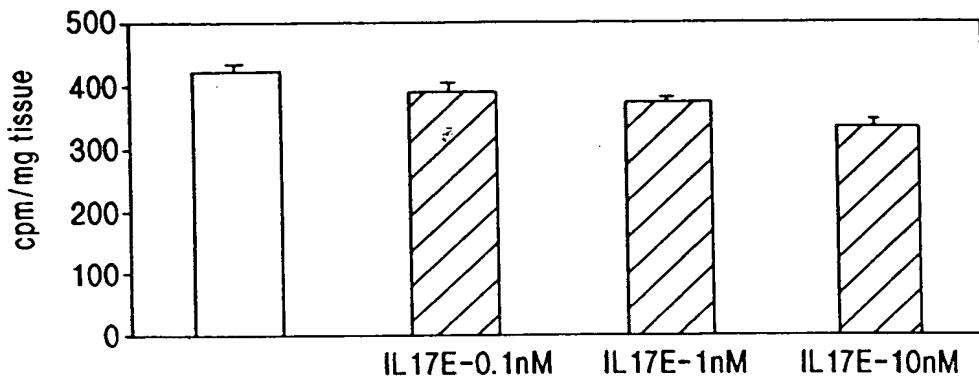
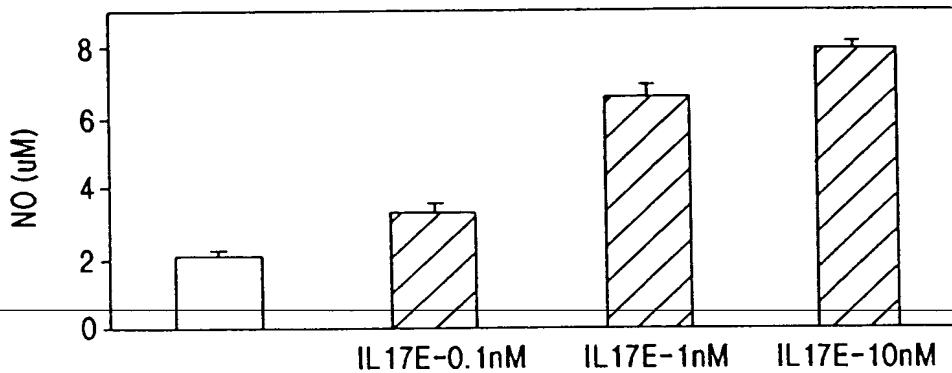
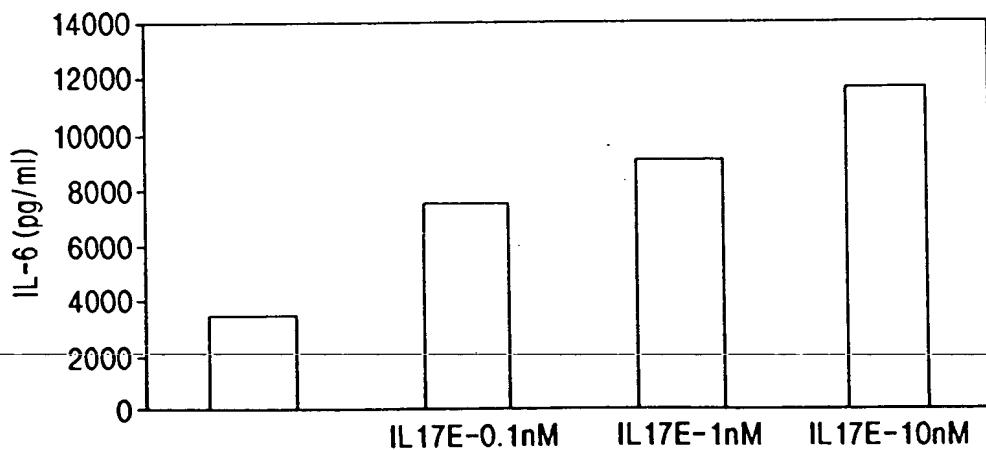
FIGURE 46**FIG. 46A****FIG. 46B****FIG. 46C**

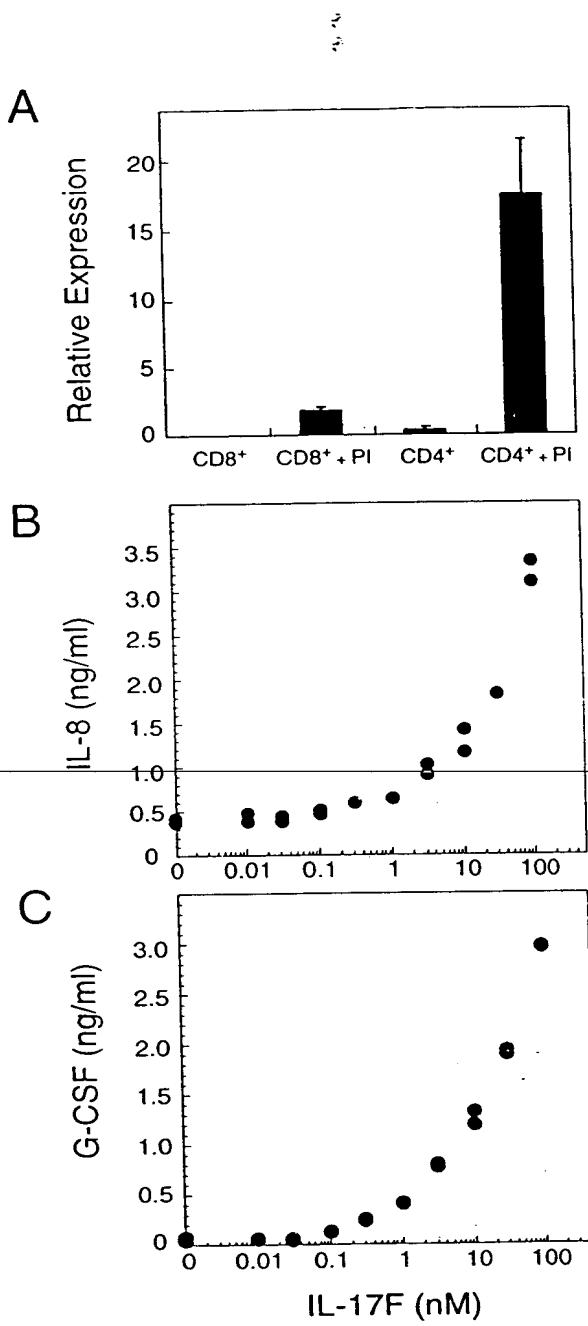
FIGURE 47

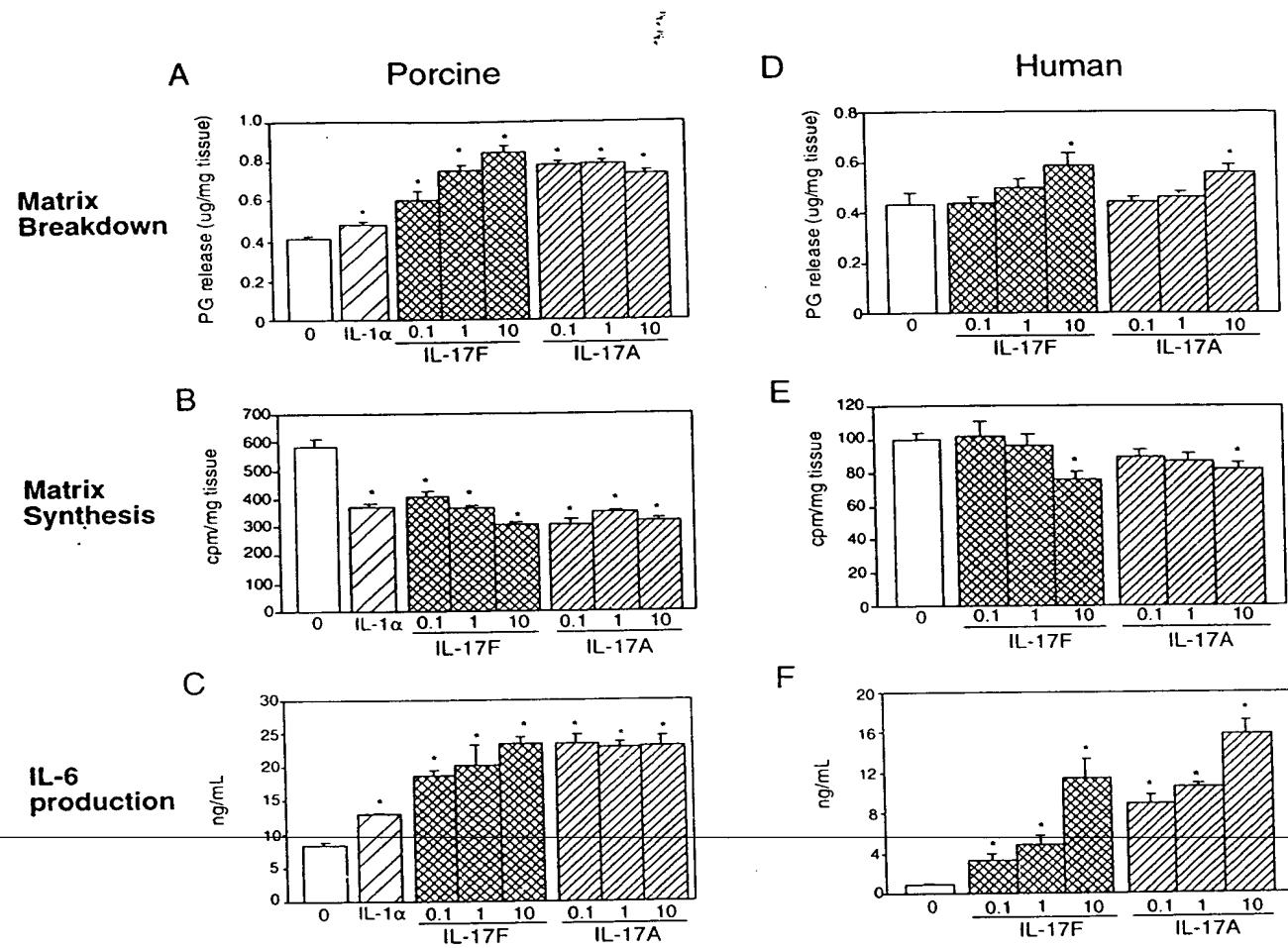
FIGURE 48

FIGURE 49

10000157-103001

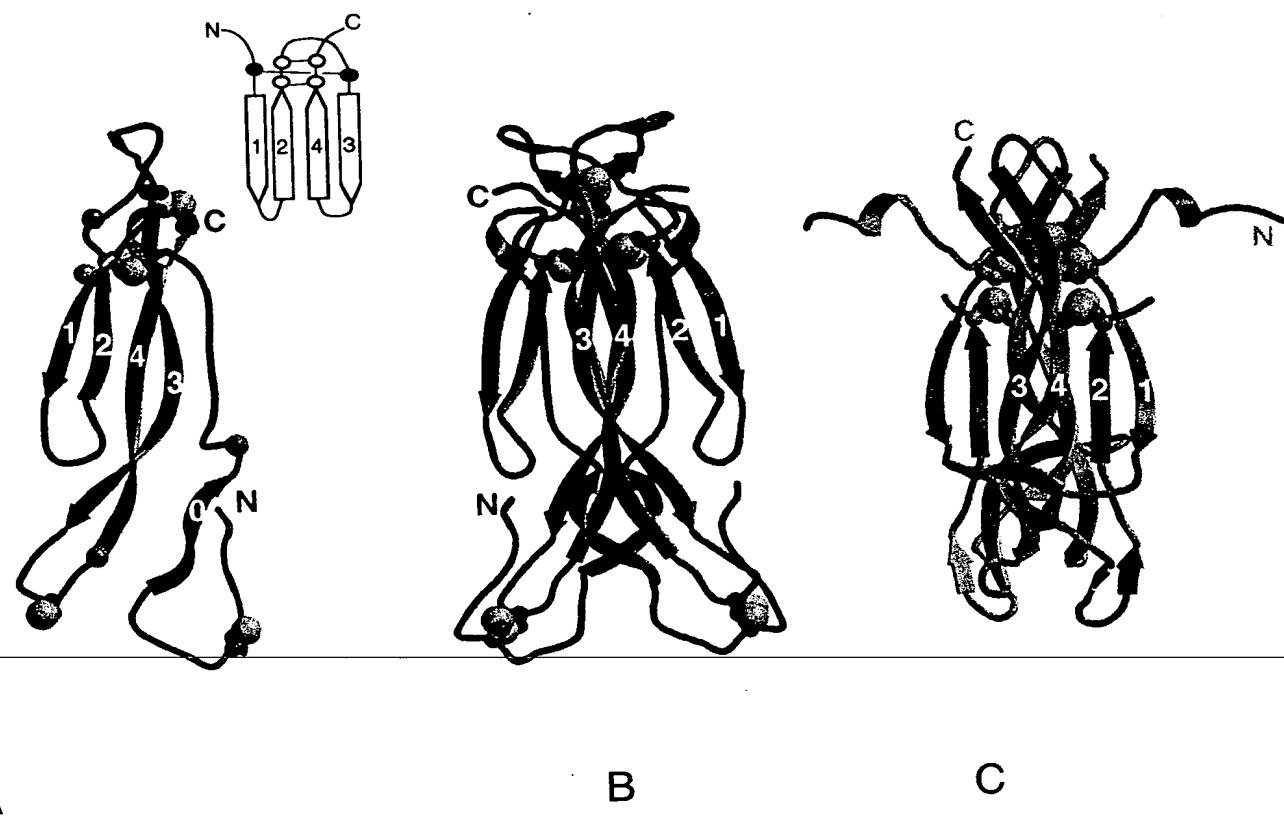


FIGURE 50

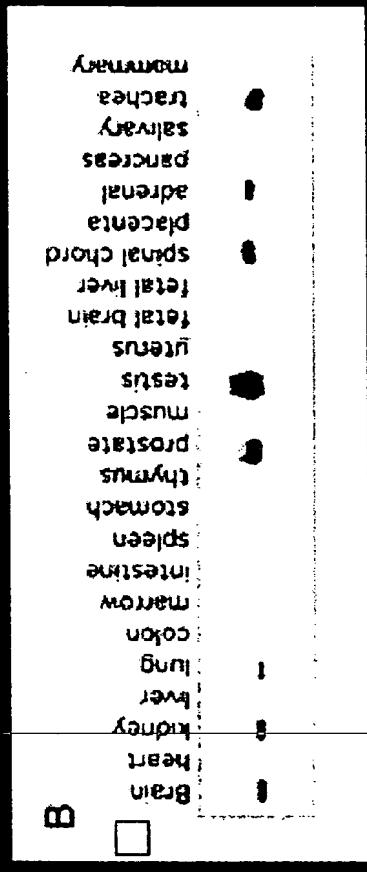
IL-17F	RKIPKVG HTFFQKPES	17
IL-17A	IVKAG ITIPRNP.G	14
IL-17B	QPRS PKSKRKQGQR	PGPLAPGPHQ	VPLDLVSRMK	PYARMEEMYER	44
IL-17C HHDPSLRGHGP	HSHGTPH.EYS	AEELPLGQAP	PHLLARGAKW	GQALPVALVS	50
IL-17E	YS HWPS	PSKG QDTSEELLRW	22

0	1			
IL-17F PPVPGG....	SMKLDI GIINENQRVS	MSRNIESRST	PWNYTVTWD	59
IL-17A PNSEDKNFPR	TVMVNLNIHN	RNTNTN..PK	PWNLHRNED	62
IL-17B NIEEMVAQLR	..NSSELAQR	K.EV....NL	PWGYSINHD	88
IL-17C SLEASHRGR	..HERPSATT	Q.PVLRPEEV	PWRYRVDTD	98
IL-17E STVPVPPLEP	..ARPNRHPE	S.RASE....	PWRYELDRD	65

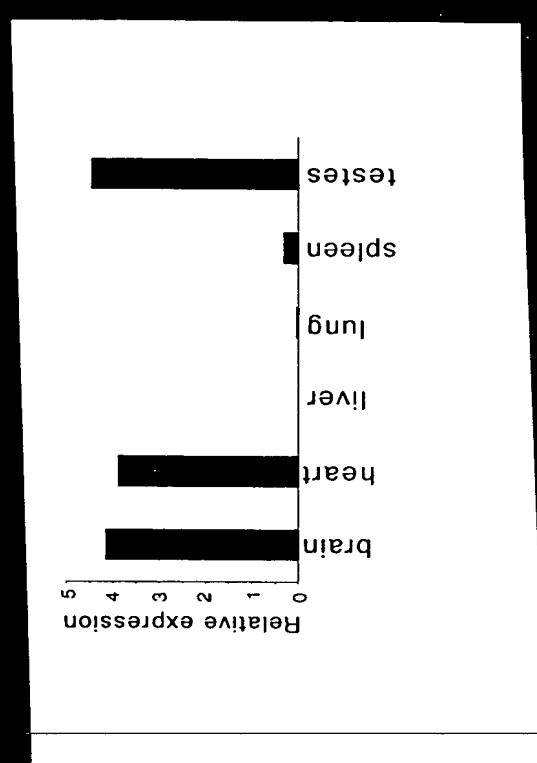
2	3			
IL-17F PNRYPSEVVQ	AQ RNLG IN A..QGKEDIS	MN VPI.QQE	TLVVRRKHQG	106
IL-17A PERYPSVIWE	AK RHLG IN A..DGNVDYH	MN VPI.QQE	ILVLRREPPH	109
IL-17B PSRIPVDLPE	AR L.LG VN PF.TMQEDRS	MV VPV.FSQ	VPVRRR...L	133
IL-17C EDRYPQKLA	AE L.RG ID AR.TGRETAA	LN VRL.LQS	LLVLR..RP	144
IL-17E LNRLPQDLYH	AR L.PH VS LQTGSHMDPR	GN ELLYHNQ	TVFYRRP...	112

4	5		
IL-17F SV.....	SFQLEK VL..VTVG T	VTPVIHHVQ	133
IL-17A PN.....	SFRLEK IL..VSVG T	VTPIVHHVA	136
IL-17B PPPRTGP.	FRQRA VMETIAVG T	IF.....	160
IL-17C SRDGSGLPT	PGAFAFHTEF IH..VPVG T	V.LPRSVAA ALE	184
IL-17E HGEKGTHKGYLER RLYRVSLA V	VRPRVMG..	145

Tissue distribution of IL-17E



IL-17E (PCR then probed with cDNA)



Taqman assay

Mill-17E transgenics are growth retarded

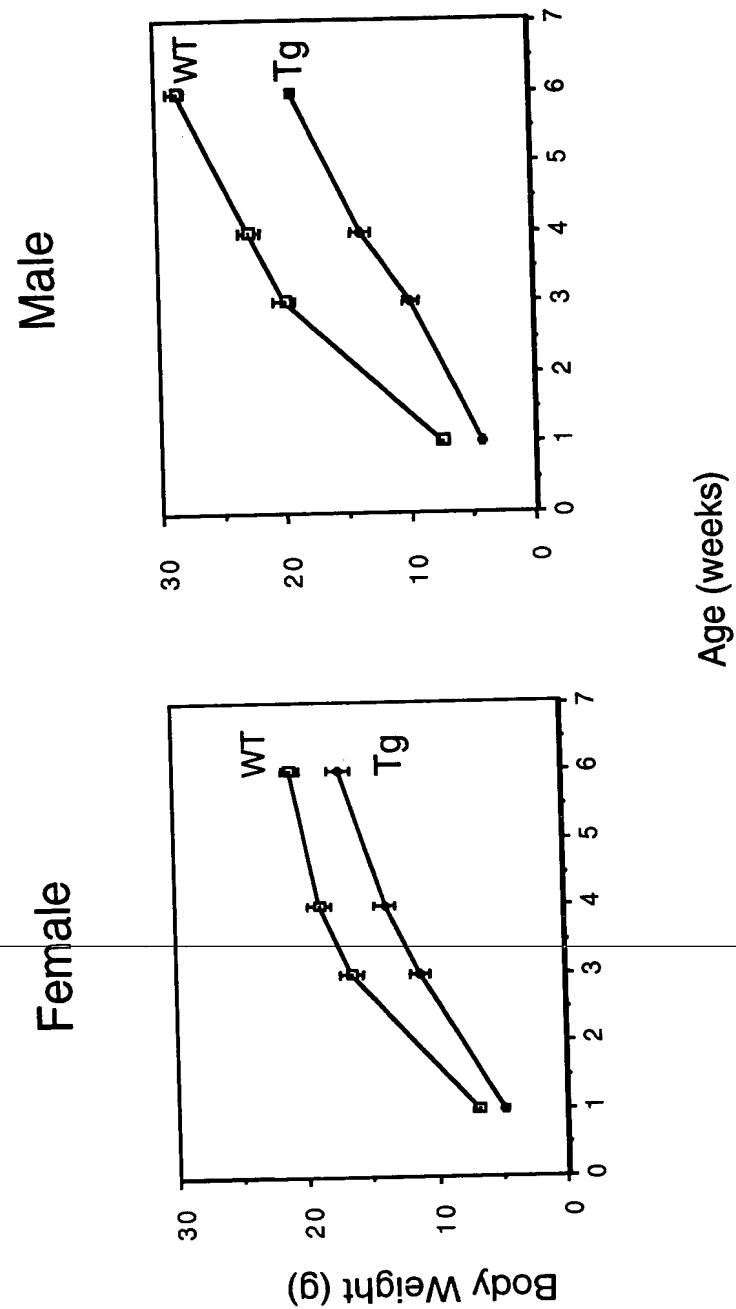


FIGURE 55

IL17E transgenics are jaundiced by 6 weeks of age

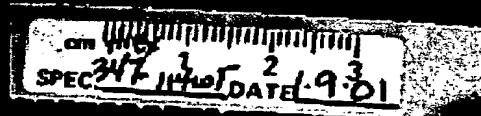


FIGURE 56

mlL-17E transgenics have elevated
total bilirubin and liver enzymes

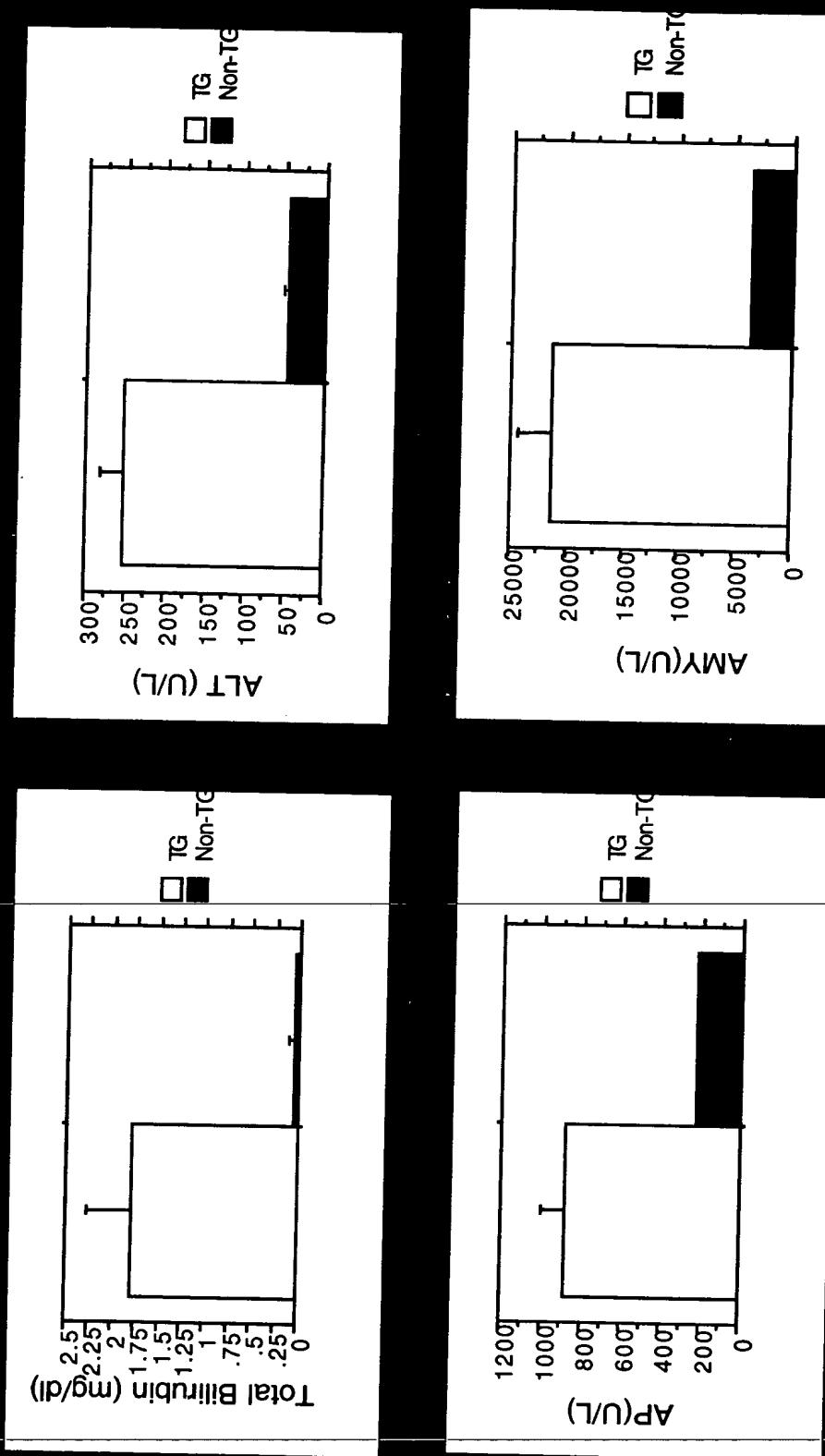


FIGURE 57

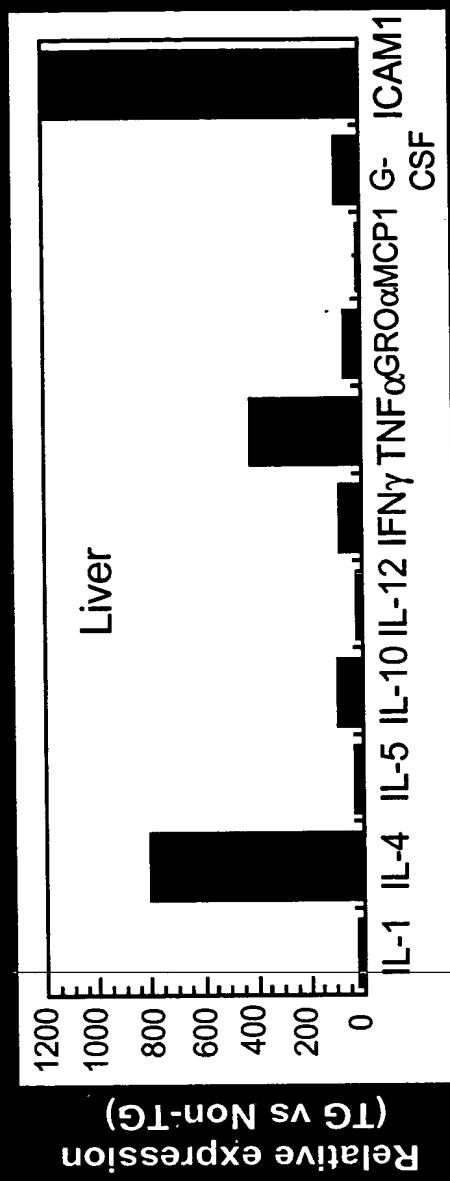
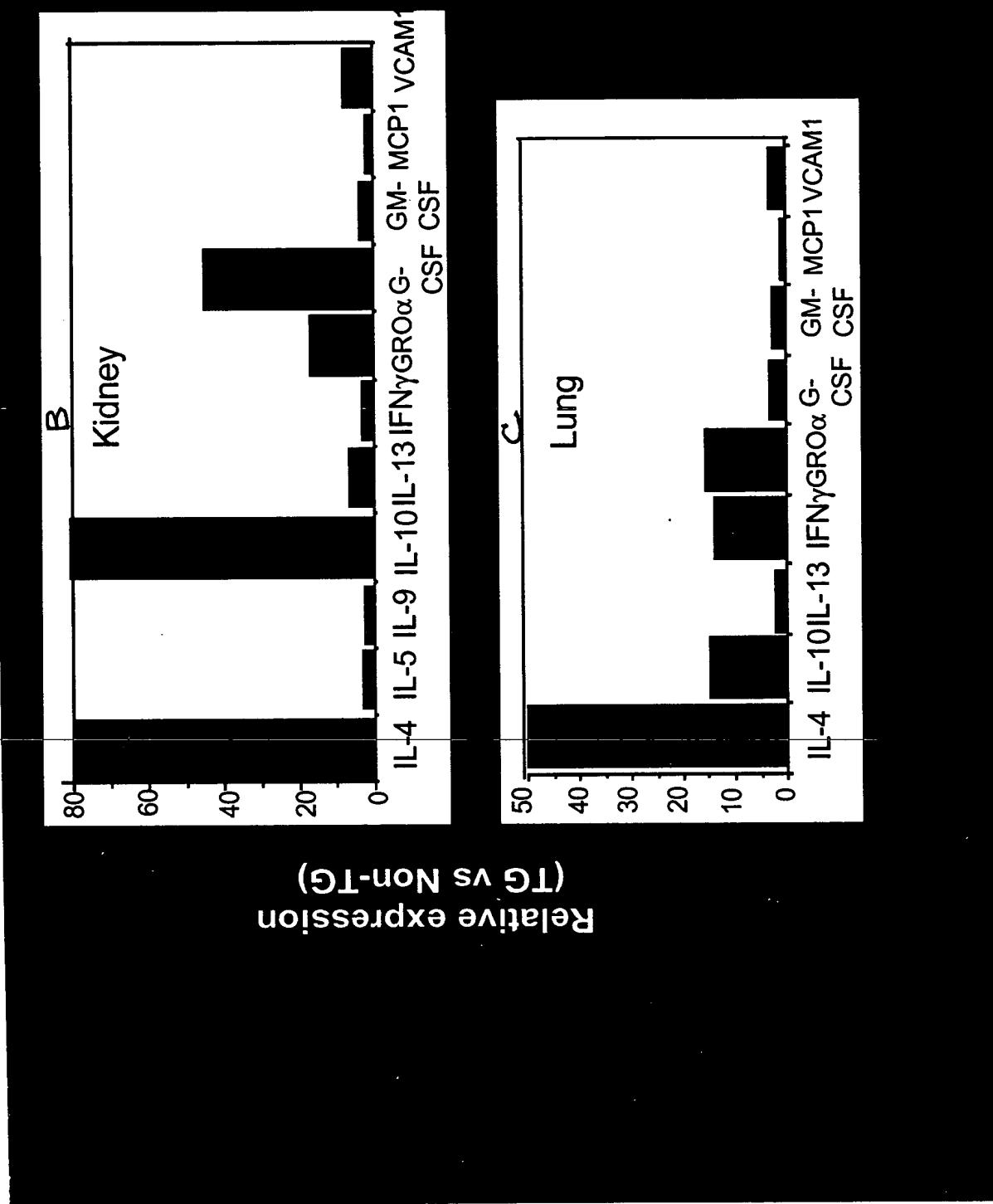


FIGURE 58A



FIGURES 58B - 58C

Gene profiling of IL-17E transgenic (Taqman)

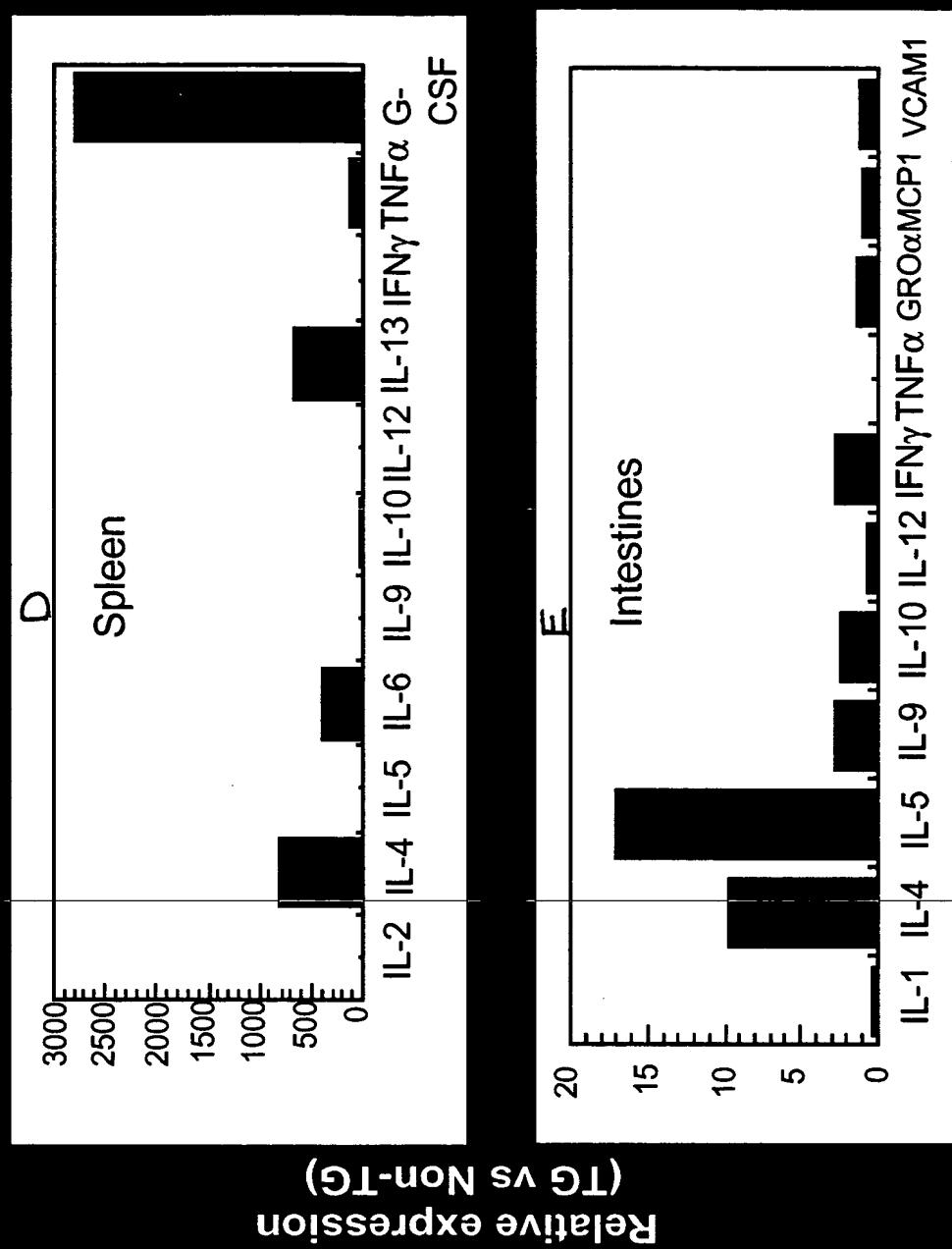


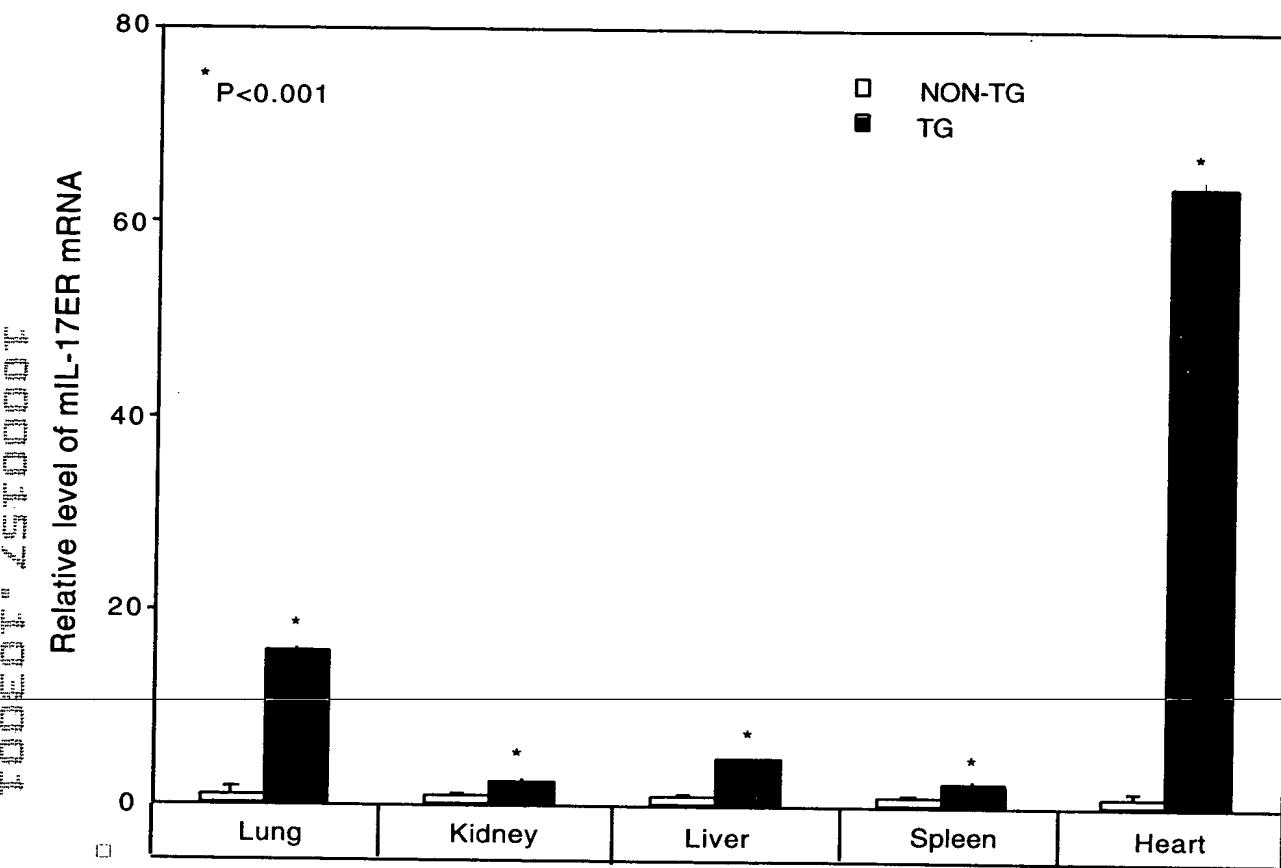
FIGURE 59

FIGURE 60

Elevated serum IL-5, IL-13 and TNF α in mIL-17E transgenics

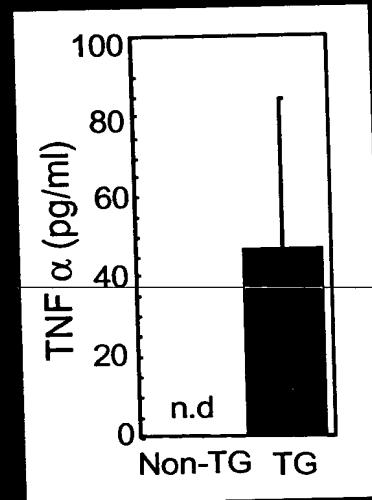
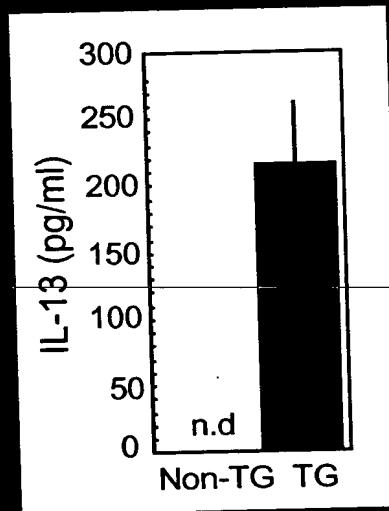
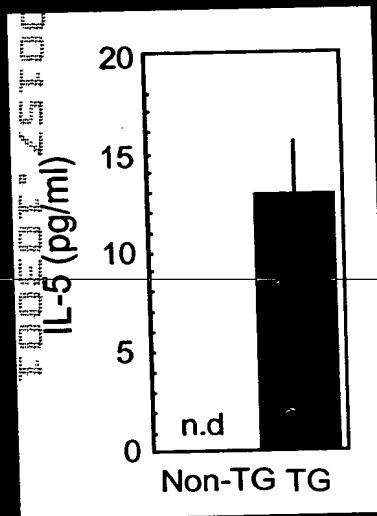


FIGURE 61

Serum IgE and IgG1, but not IgG2a is elevated in mIL-17E transgenics

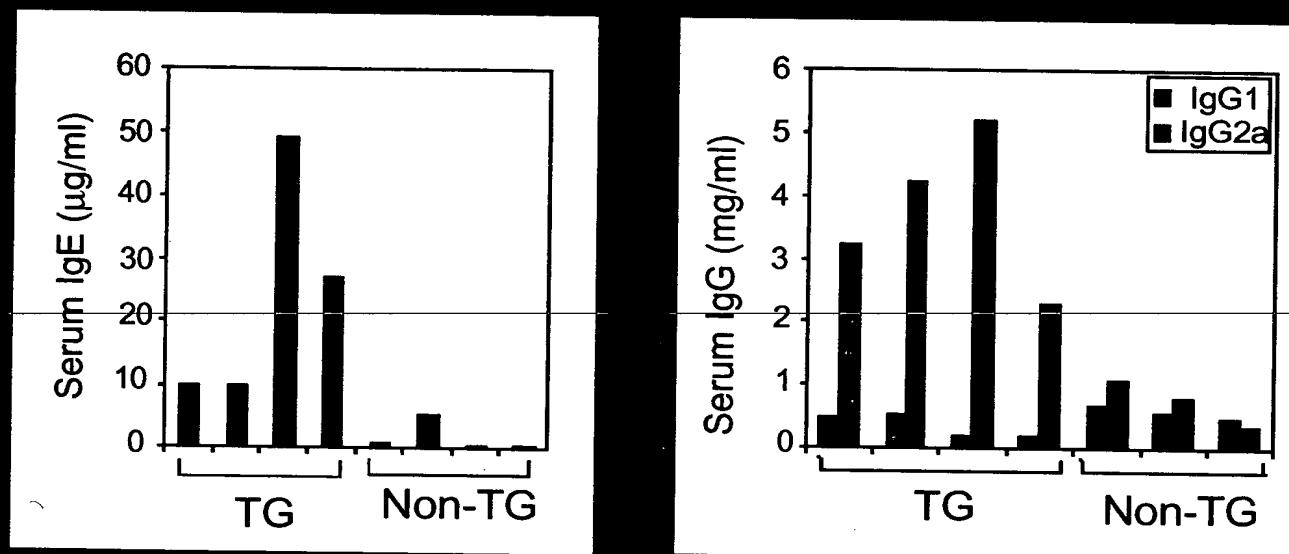


FIGURE 62

Neutrophilia in mIL-17E transgenics (8 wks, PBMC by FACS)

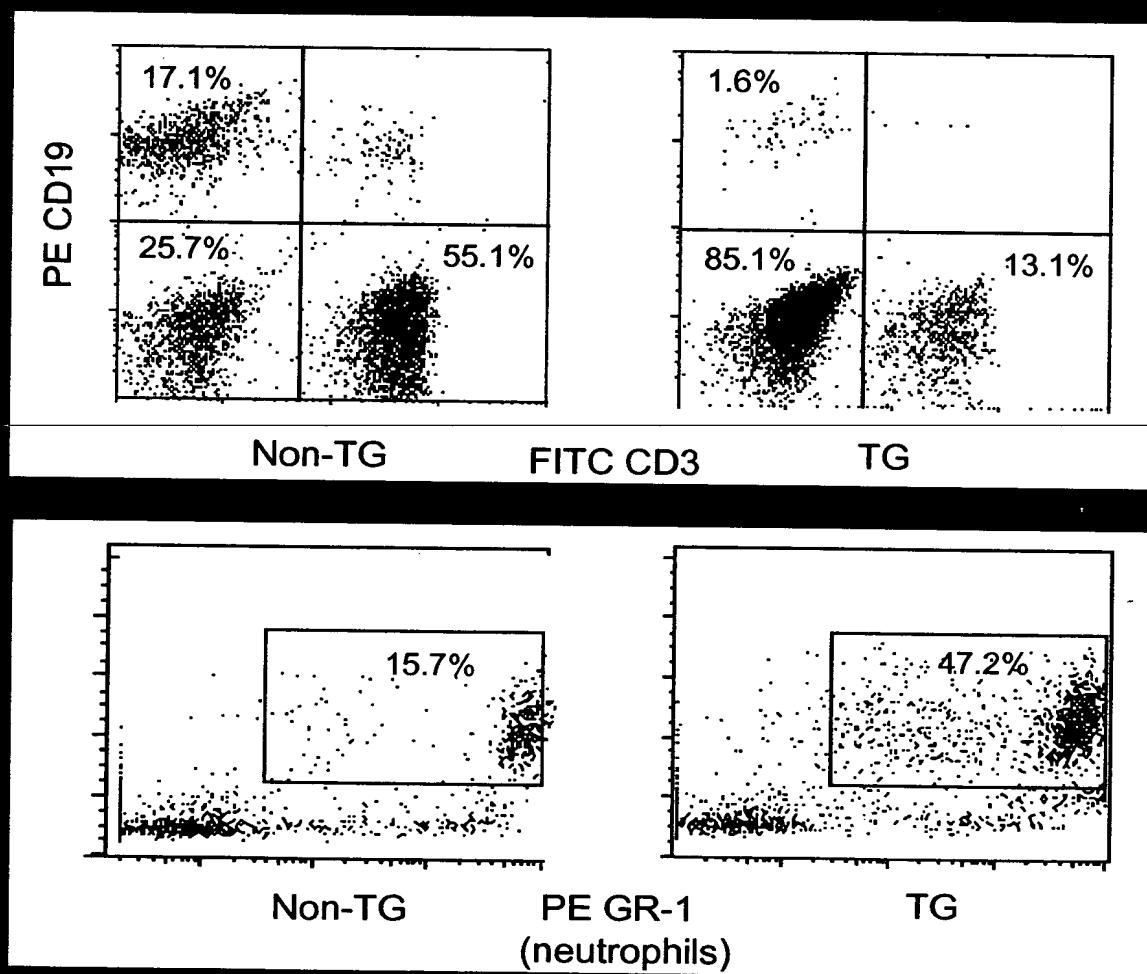


FIGURE 63

Neutrophilia and eosinophilia in mIL-17E transgenics (hematology)

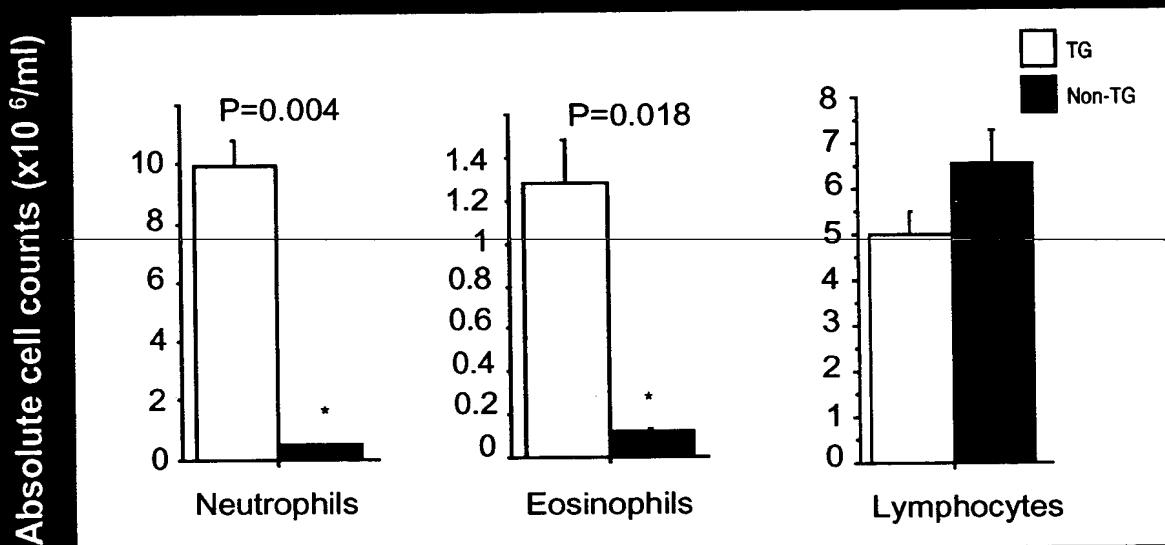


FIGURE 64

G-CSF is elevated
in mIL-17E transgenics

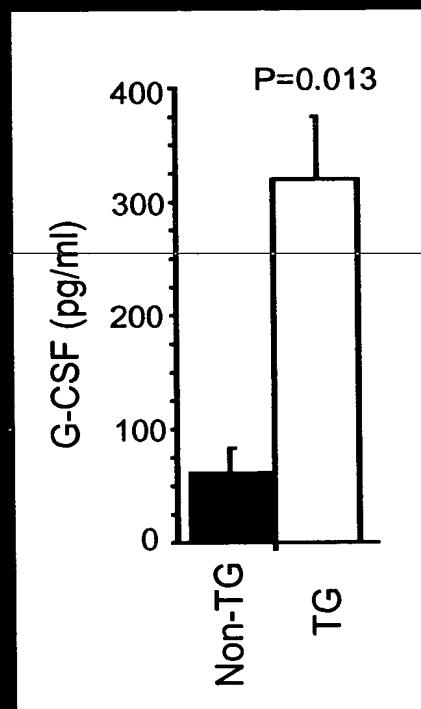


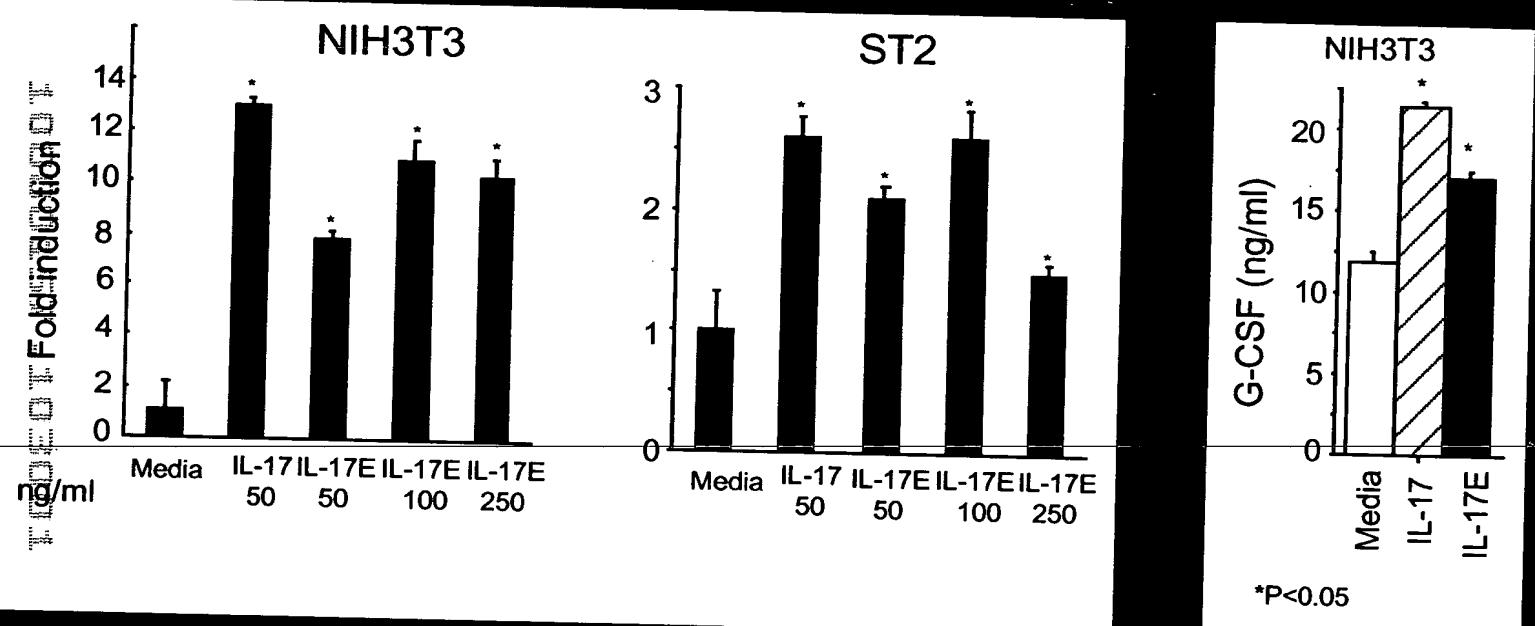
FIGURE 65

FIGURE 66

